(12) INTERNATIONAL APPLICATION PUBLISHED PURSUANT TO THE INTERNATIONAL PATENT COOPERATION TREATY

(19) INTERNATIONAL BUREAU OF THE WORLD INTELLECTUAL PROPERTY OFFICE
(43) DATE OF DISCLOSURE

February 1, 2001 (01.02.2001)

PCT

(10) INTERNATIONAL DISCLOSURE NO.
WO 01/07031 A1

(51) **International Patent Classification**[7]:
A61K 31/085, 31/09, 31/12, 31/343, 31/352, 31/353, A61P 37/04, 43/00, C07D 307/79, 307/80, 311/64, C07C 43/215, 43/23, 49/84, 69/157

(21) **International File No.:** PCT/JP00/05001
(22) **International Application Date:** July 26, 2000
(25) **Language of International Application:** Japanese
(26) **Language of International Disclosure:** Japanese

(30) **Priority Data:**
Application 11/211399 July 26, 1999 JP

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(81) Designated States (Domestic) (Unless otherwise designated, all types of domestic protection permitted): AE, AG AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

(84) Designated Countries (Extended) (Unless otherwise designated, all types of extended protection permitted): ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasia (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, CH, CY, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GW, ML, MR, NE, SN, TD, TG)

Appended Publications
With international search report
Prior to expiration of deadline provided for amendments to claims. Publication is repeated in the event amendments are received.

Consult "Guidance notes for codes and abbreviations" cited in the foreword of each PCT gazette that is periodically issued with reference to the two-character codes and other abbreviations.

(54) **Title: Benzene derivatives and immunopotentiating compositions or drug-sensitivity restoring agents containing the same**

(57) Abstract: The present invention provides specific compounds and compositions for preventing or treating diseases associated with immune function failures.
Benzene derivative compounds, salts thereof or hydrates thereof have immunopotentiating effects, and are expected to be efficacious as biological defense mechanism accelerators by potentiating the lymphocyte function and potentiating the bone marrow function.

Specification

Benzene derivatives and immunopotentiating compositions or drug-sensitivity restoring agents containing the same

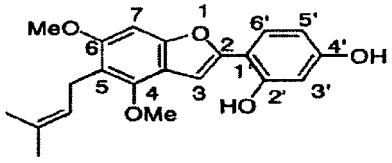
Technical Field of Invention

(Technical Field Associated with Invention)

The present invention concerns the field of medicine, veterinary medicine (livestock medicine, fisheries medicine). Specifically, it concerns benzene derivatives as well as compositions having immunopotentiating activity containing them for preventing or treating diseases accompanying immune function failure. The present invention also concerns the use of compositions having immunopotentiating activity for producing these compositions as well as methods of treatment using these compositions.

The present invention also concerns compounds that can surmount the acquired resistance of pathogenic microorganisms to restore the activity of anti-pathogenic microorganism agents to the level of drug sensitivity as well as drug sensitivity restorative agents. Concretely, the present invention concerns agents that restore the sensitivity of pathogenic microorganisms that exhibit multi-drug resistance to antibiotics, especially Pseudomonas, to drugs. The present invention concerns drug sensitivity restorative agents comprising the compound represented in general formula (I) below as well as salts thereof.

More concretely, the present invention provides a drug sensitivity restorative agent comprising the compound represented in formula (M) as well as salts thereof.



formula (M)

The present invention provides medicinal compositions that contain said sensitivity restorative agents and antibiotics. The present invention also concerns the use of compounds of general formula (I) for producing these drug sensitivity restorative agents as well as methods of treatment using these drug sensitivity restorative agents.

Background Technology

(Related Art)

Conventional technology concerning immunopotentiating agents is explained first.

In recent years, various types of immunopotentiating agents (principal cellular constituent: Muramyldipeptides, OK-432, principal mushroom constituents: Krestin, lentinan; synthetic compounds: Levamisole, bestatin, peptides: G-CSF, GM-CSF) have been used for the prevention or treatment of diseases accompanying decline in biological defense mechanisms such as opportunistic infections, radiation-induced disorders, cancer as well as infections in patients with

cancer or HIV, but various adverse drug reactions have been discovered associated with many of these drugs. Consequently, compounds having a novel framework that permits oral administration without bringing about the serious adverse drug reactions found in known immunopotentiating agents are desired.

Conventional technology associated with drug sensitivity restorative agents is explained below.

Humans have developed various novel antibiotics or anti-pathogenic microorganism agents following the advent of penicillin, and methods of treating infections caused by pathogenic microorganisms have been established. However, the life of novel anti-pathogenic microorganism agents has been short because resistant pathogenic microorganisms soon appeared. For that reason, the development of multi-drug resistance by pathogenic microorganisms became a serious problem and surmounting it became an important issue. Among these infections, Pseudomonas infections especially tended to be highly refractory and multi-drug resistant infectious bacteria rapidly developed, complicating treatment of infections caused by them. The development of resistance by microorganisms in this specification is termed decline in drug sensitivity. Furthermore, the subsequent decline in the resistance of microorganisms that have developed such resistance is termed restoration of drug sensitivity.

Factors associated with the mechanism through which Pseudomonas develops drug resistance include decrease in membrane permeability (LPS, porin mutation), change in the site of activity (penicillin-bound protein PBP: change in drug compatibility with peptidoglycan synthetase), drug deactivation enzymes (production of β-lactamase, aminoglycoside modifying enzymes), DNA gyrase mutation, excretion of endobacillary drugs by drug excretion system). In recent years, attention has been focused on the drug excretion system as the mechanism through which bacteria develop multi-drug resistance, specifically, on the production of drug transporters, and research on the molecular level has been vigorously carried out. The acquisition by Pseudomonas of moderate resistance to various types of antibiotics due to this action has been clarified, and the production of the drug excretion system, specifically, of drug transporters, has been shown to participate in the spontaneous development of resistance by Pseudomonas (J. bacteriol. 175: 7363-7372, 1993) (Biochem. Biophys. Res. Commun. 210: 356-362, 1995). The development of an inhibitor of such drug excretion transporters would restore sensitive strains of Pseudomonas that had developed low drug sensitivity as well as the antibacterial activity of antibiotics. This promises the development of drug excretion transporters that could elevate the therapeutic effects.

The compound L-phenylalanine-L-arginyl-β-naphthylamide presented in WO 96/33284 is an example of a compound that inhibit drug excretion transporters. This is a dipeptide compound that lowers the MIC of laboratory mutant overproducing OprM (K385) and its standard strain (PA01) to piperacillin, ceftazidime, and new quinolone-7 agents such as such as chloramphenicol, tetracycline, ofloxacin. The compound Micacocidin presented in WO99/61021 has also been reported as a compound having similar effects.

However, the immunopotentiating effects of compounds represented by general formula (I) below and of salts thereof have been unknown in the field of immunopotentiating agents and drug sensitivity restorative agents, and the existence of drug sensitivity restorative effects was also unknown.

(Problems Solved by the Invention)

One aspect of the present invention is to solve aforementioned problems by providing a compound and having immunopotentiating effects.

Another aspect of the present invention that is based on the circumstances associated with aforementioned development of drug resistance by microorganisms surmounts the resistance acquired by pathogenic microorganisms in order to provide drug sensitivity restorative agents capable of restoring the activity of anti-pathogenic microorganism agents to the level of drug sensitive strains.

Disclosure of Invention

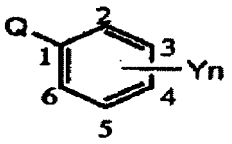
(Means of Solving the Problems)

The inventors have continued thorough research, the results of which culminated in the discovery of the fact that the compound discussed below has immunopotentiating effects. Specifically, the present invention concerns immunopotentiating compositions containing the compound represented by general formula (I) as well as salts thereof.

In addition, the results of further research by the inventors into novel drug sensitivity restorative agents revealed that compounds represented by general formula (I) below as well as salts thereof, especially compounds represented by formula (M) below as well as salts thereof have drug sensitivity restorative effects. That discovery completed the present invention. Specifically, the present invention concerns drug sensitivity restorative agents containing the compound represented by general formula (I) below as well as salts thereof. The compound represented by formula (M) below in the specification is termed "compound (M)".

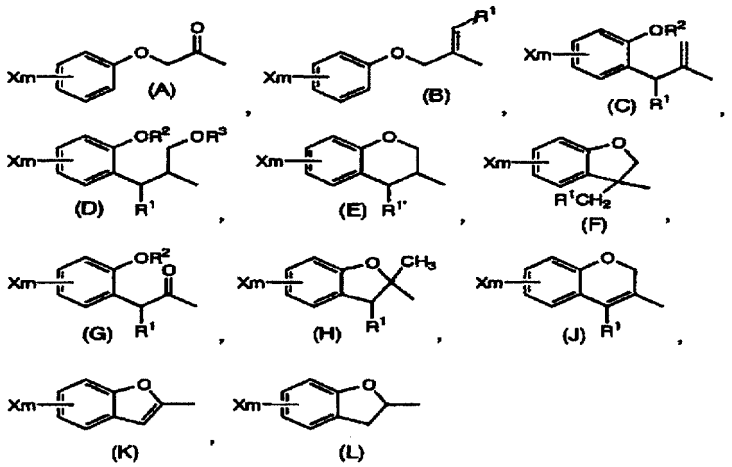
In addition, the present invention provides the following compositions, compounds, and their production method.

(1) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I):



(I)

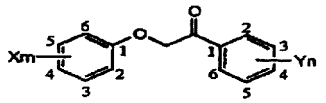
[In the formula, Q represents the following



(In the formula, X represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
R^1 and $R^{1'}$ represent hydrogens or alkyls;
R^2 and R^3 represent hydrogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, tri-substituted silyls, optionally substituted acyls, optionally substituted amino carbonyls or mono-substituted sulfonyls;
and m represents an integer of 0 to 4);
Y represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, monosubstituted sulfinyls,

monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
and n represents an integer of 0 to 5;
however, position 5 and position 7 Xm, position 2 and position 4 Yn in formula (E) may all be identical or different hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, or tri-substituted silyloxys, in which cases $R^{1'}$ is not a hydrogen].

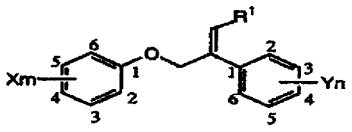
(2) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-A):



(I-A)

(In the formula, X, Y, m and n have the same significance as in aforementioned section (1)).

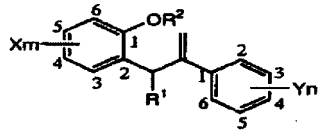
(3) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-B):



(I-B)

(In the formula, X, Y, R^1, m and n have the same significance as in aforementioned section (1)).

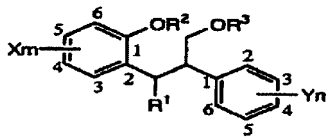
(4) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-C):



(I-C)

(In the formula, X, Y, R^1, R^2, m and n have the same significance as in aforementioned section (1)).

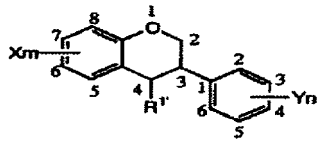
(5) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-D):



(I-D)

(In the formula, X, Y, R^1, R^2, R^3, m and n have the same significance as in aforementioned section (1)).

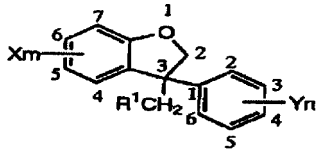
(6) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-E):



(I-E)

(In the formula, X, Y, R^1, m and n have the same significance as in aforementioned section (1)).

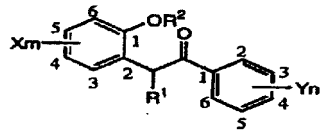
(7) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-C):



(I-F)

(In the formula, X, Y, R^1, m and n have the same significance as in aforementioned section (1)).

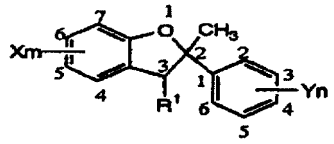
(8) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-G):



(I-G)

(In the formula, X, Y, R^1, R^2, m and n have the same significance as in aforementioned section (1)).

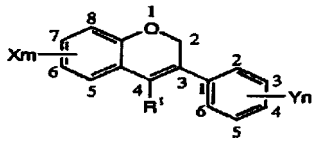
(9) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-H):



(I-H)

(In the formula, X, Y, R^1, R^2, m and n have the same significance as in aforementioned section (1)).

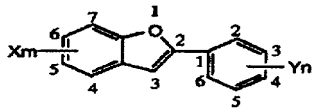
(10) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-J):



(I-J)

(In the formula, X, Y, R^1, m and n have the same significance as in aforementioned section (1)).

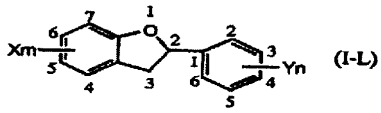
(11) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-K):



(I-K)

(In the formula, X, Y, m and n have the same significance as in aforementioned section (1)).

(12) A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-L):



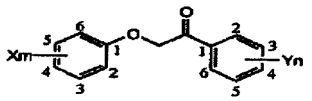
(I-L)

(In the formula, X, Y, m and n have the same significance as in aforementioned section (1)).

(13) The compositions stated in aforementioned section (1) wherein X represents halogens, alkyls, alkenyls, hydroxys, optionally substituted alkoxys, Y represents halogens, alkyls, haloalkyls, aryls, hydroxys, optionally substituted alkoxys, alkenyloxys, tri-substituted silyloxys, or nitros, and m represents an integer of 0 to 3 while n represents an integer of 0 to 2.

(14) The compositions stated in aforementioned section (1) wherein X represents chloros, methyls, hydroxys, methoxys or prenyloxys, Y represents fluoros, methyls, trifluoromethyls, phenyls, hydroxys, methoxys, prenyloxys, n-hexyloxys, 2-phenoxyethoxys, 2-(1,3-dioxoran-2-yl) ethoxys, benzyloxys, or nitros, while m represents an integer of 0 to 3 and n represents an integer of 0 to 2.

(15) Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-A):

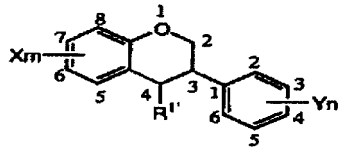


(I-A)

(In the formula, X represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
Y represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;

m represents an integer of 1 to 4 and n represents an integer of 1 to 5)

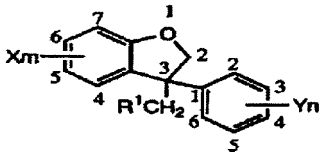
(16) Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-E):



(I-E)

(In the formula, X, Y, R^1, m and n have the same significance as in aforementioned section (15), $R^{1'}$ represents hydrogens or alkyls, but position 5 and position 7 Xm, position 2 and position 4 Yn in formula (I-E) may all be identical or different hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys or tri-substituted silyloxys, in which cases $R^{1'}$ is not a hydrogen).

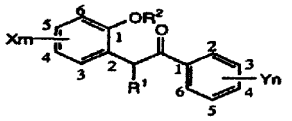
(17) Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-F):



(I-F)

(In the formula, X, Y, m and n have the same significance as in aforementioned section (15), $R^{1'}$ represents hydrogens or alkyls).

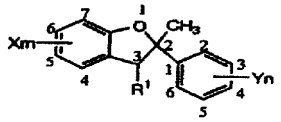
(18) Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-G):



(I-G)

(In the formula, X, Y, m, n and R^1 have the same significance as in aforementioned section (15), R^2 represents optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, tri-substituted silyls, optionally substituted acyls, optionally substituted amino carbonyls, or mono-substituted sulfonyls).

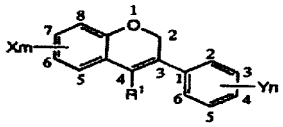
(19) Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-H):



(I-H)

(In the formula, X, Y, m and n have the same significance as in aforementioned section (15), R^1 has the same significance as in aforementioned (17).

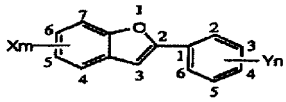
(20) Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-J):



(I-J)

(In the formula, X, Y, m and n have the same significance as in aforementioned section (15), R^1 has the same significance as in aforementioned (17).

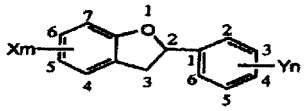
(21) Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-K):



(I-K)

(In the formula, X, Y, m and n have the same significance as in aforementioned section (15), but Yn is not 4-dihydroxy when Xm represents 4,6-dimethoxy-5-prenyl).

(22) Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-L):

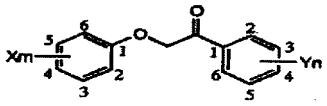


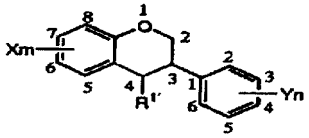
(I-L)

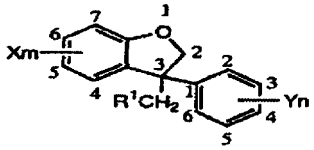
(In the formula, X, Y, m and n have the same significance as in aforementioned section (15).

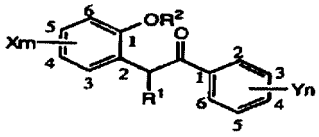
(23) Compounds represented by the following formulas, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,

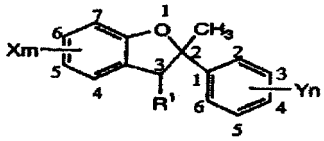
general formulas (I-A), (I-E), (I-F), (I-G), (I-H), (I-J), (I-K), or (I-L).

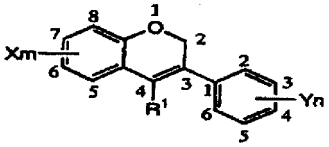

(I-A)

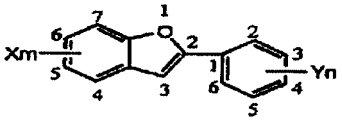

(I-E)

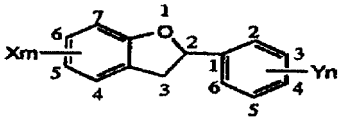

(I-F)


(I-G)


(I-H)


(I-J)


(I-K)


(I-L)

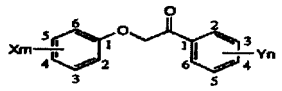
(In the formula, X represents halogens, alkyls, alkenyls, hydroxys, optionally substituted alkoxys;

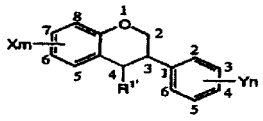
Y represents halogens, alkyls, haloalkyls, aryls, hydroxys, optionally substituted alkoxys, alkenyloxys, tri-substituted silyloxys, or nitros;
m represents an integer of 0 to 3,
n represents an integer of 0 to 2;
$R^{1'}$ represents hydrogens or alkyls, however, position 5 and position 7 Xm as well as position 2 and position 4 Yn in formula (I-E) may be identical or different hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, in which cases $R^{1'}$ is not hydrogen;
R^1 represents hydrogens or alkyls;
R^2 represents optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, tri-substituted silyls, optionally substituted acyls, optionally substituted amino carbonyls, or mono-substituted sulfonyls;
however, when Xm in formula (I-K) is 4,6-dimethoxy-5-prenyl, Yn is not 2,4-dihydroxy).

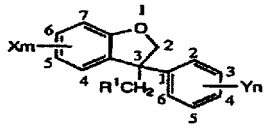
(24) Compounds presented in aforementioned section (23), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof wherein X represents chloros, methyls, hydroxys, methoxys, or prenyloxys, Y represents fluoros, methyls, trifluoromethyls, phenyls, hydroxys, methoxys, prenyloxys, n-hexyloxys, 2-phenoxyethoxys, 2-(1,3-dioxolan-2-yl) ethoxys, benzyloxys, or nitros, m represents an integer of 0 to 3, n represents an integer of 0 to 2.

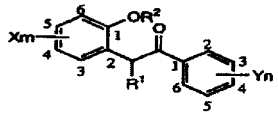
(25) Compounds presented in aforementioned section (23), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof wherein Xm represents 4-chloro, 3-methoxy, 4-methoxy, 5-methoxy, 3,5-dimethoxy, or 3,5-dimethoxy-4-prenyloxy, Yn represents 4-fluoro, 4-methyl, 2-trifluoromethyl, 2,4-dimethyl, 2-phenyl, 4-phenyl, 2-hydroxy, 2,4-dihydroxy, 2-prenyloxy, 2-n-hexyloxy, 2-benzyloxy, 3-benzyloxy, 4-benzyloxy, 2-benzyloxy-4-hydroxy, 2,4-dibenzyloxy, 3-(1,3-dioxolan-2-yl) ethoxy, 3- phenoxyethoxy, or 3-nitro (however, the names of the individual substitution positions conform with the nomenclature method of the substitution positions in general formula (I-A).

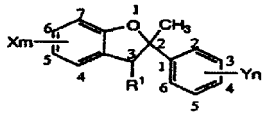
(26) A composition containing compounds represented by the following formulas, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof as the active ingredient: general formulas (I-A), (I-E), (I-F), (I-G), (I-H), (I-J), (I-K), or (I-L).

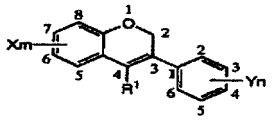

(I-A)

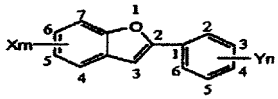

(I-E)

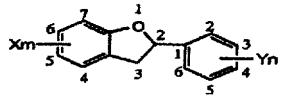

(I-F)


(I-G)


(I-H)


(I-J)


(I-K)

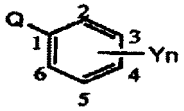

(I-L)

(In the formula, X represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, mono-substituted sulfinyls, mono-substituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
Y represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys,

optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, mono-substituted sulfinyls, mono-substituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
m represents an integer of 1 to 4;
n represents an integer of 1 to 5;
$R^{1'}$ represents hydrogens or alkyls, however, position 5 and position 7 Xm as well as position 2 and position 4 Yn in formula (I-E) may be identical or different hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, in which cases $R^{1'}$ is not hydrogen;
R^1 represents hydrogens or alkyls;
R^2 represents optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, tri-substituted silyls, optionally substituted acyls, optionally substituted amino carbonyls, or mono-substituted sulfonyls).

(27) The compositions presented in aforementioned section (26) that have immunopotentiating effects.

(28) The use of compounds of general formula (I), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof to produce compositions having immunopotentiating effects:

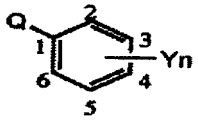


(I)

(In the formula, Q, Y, and n have the same significance as in aforementioned section (1)).

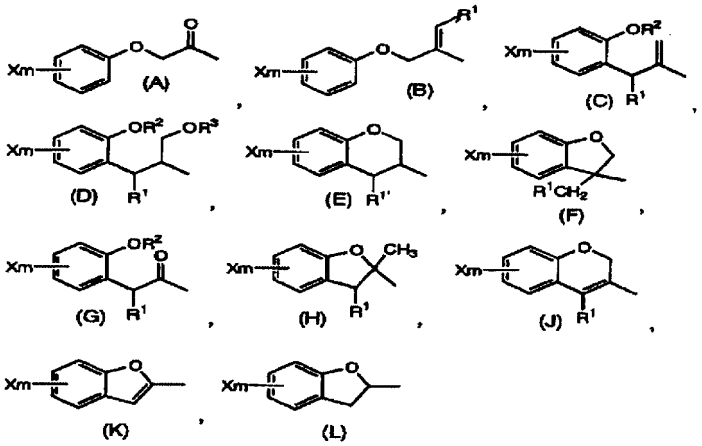
(29) A method of incorporating the step of administering the compositions stated in aforementioned section (1) to a subject of examination in the method of activating the immunity of said subject of examination.

(30) Drug sensitivity restorative agents containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof.
general formula (I)



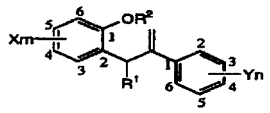
(I)

[In the formula, Q represents the following



(In the formula, X represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, mono-substituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
R^1 and $R^{1'}$ represent hydrogens or alkyls;
R^2 and R^3 represent hydrogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, tri-substituted silyls, optionally substituted acyls, optionally substituted amino carbonyls or mono-substituted sulfonyls;
and m represents an integer of 0 to 4);
Y represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
and n represents an integer of 0 to 5; however, position 5 and position 7 Xm as well as position 2 and position 4 Yn in formula (E) may all be identical or different hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, or tri-substituted silyloxys, in which cases $R^{1'}$ is not a hydrogen].

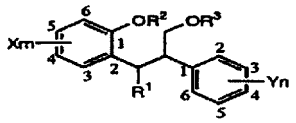
(31) Drug sensitivity restorative agents containing compounds represented by general formula (I-C), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof



(I-C)

(In the formula, X, Y, R^1, R^2, m and n have the same significance as in aforementioned section (30)).

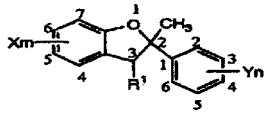
(32) Drug sensitivity restorative agents containing compounds represented by general formula (I-D), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof



(I-D)

(In the formula, X, Y, R^1, R^2, R^3, m and n have the same significance as in aforementioned section (30)).

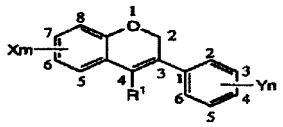
(33) Drug sensitivity restorative agents containing compounds represented by general formula (I-H), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof



(I-H)

(In the formula, X, Y, R^1, m and n have the same significance as in aforementioned section (30)).

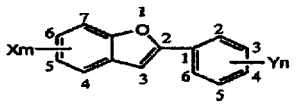
(34) Drug sensitivity restorative agents containing compounds represented by general formula (I-J), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof



(I-J)

(In the formula, X, Y, R^1, m and n have the same significance as in aforementioned section (30)).

(35) Drug sensitivity restorative agents containing compounds represented by general formula (I-K), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof

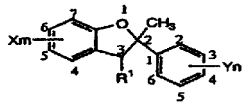

(I-K)

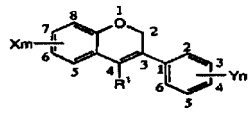
(In the formula, X, Y, m and n have the same significance as in aforementioned section (30)).

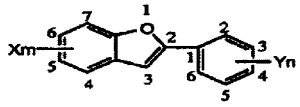
(36) Drug sensitivity restorative agents presented in aforementioned section (30) wherein X represents halogens, alkyls, alkenyls, hydroxys, optionally substituted alkoxys, Y represents halogens, alkyls, haloalkyls, aryls, hydroxys, optionally substituted alkoxys, alkenyloxys, tri-substituted silyloxys, or nitros, and m represents an integer of 0 to 3 while n represents an integer of 0 to 2.

(37) Drug sensitivity restorative agents presented in aforementioned section (30) wherein X represents chloros, methyls, hydroxys, methoxys, or prenyloxys, Y represents fluoros, methyls, trifluoromethyls, phenyls, hydroxys, methoxys, prenyloxys, n-hexyloxys, 2-phenoxyethoxys, 2-(1,3-dioxolan-2-yl) ethoxys, benzyloxys, or nitros, m represents an integer of 0 to 3, n represents an integer of 0 to 2.

(38) Drug sensitivity restorative agents containing compounds represented by the following formulas, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof as the active ingredient:
general formulas (I-H), (I-J), or (I-K)


(I-H)


(I-J)


(I-K)

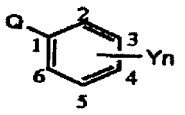
(In the formula, X represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, mono-substituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;

Y represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
m represents an integer of 1 to 4;
n represents an integer of 1 to 5;
R^1 represents hydrogens or alkyls;
however, when Xm in formula (I-K) is 4,6-dimethoxy-5-prenyl, Yn is not 2,4-dihydroxy).

(39) Drug sensitivity restorative agents presented in aforementioned section (30) that restore the sensitivity of Pseudomonas to drugs.

(40) Drug sensitivity restorative agents presented in aforementioned section (30) that restore sensitivity that had been reduced by OprM overproduction.

(41) The use of compounds of general formula (I), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof to produce drug sensitivity restorative agents:



(I)

(In the formula, Q, Y, and n have the same significance as in aforementioned section (30)).

(42) A method of incorporating the step of administering the drug sensitivity restorative agents stated in aforementioned section (30) to an subject of examination in the method of restoring the sensitivity of said subject of examination to drugs.

Best Mode for Implementing Invention
(Embodiments of Invention)

The term "alkyl" used alone or in combination with other terms in the specification connotes a straight-chain or branched-chain monovalent hydrocarbons with 1 to 20 carbon atoms. Examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, iso-hexyl, n-heptyl, n-octyl, etc. C1 to C6 alkyls are preferable.

The term "alkenyl" used alone or in combination with other terms in the specification connotes a straight-chain or branched-chain monovalent hydrocarbons with one, two or more double bonds and 2 to 12 carbon atoms. Examples include vinyl, allyl, propenyl, crotonyl, prenyl, and various butenyl isomers. C2 to C6 alkenyls are preferable.

The term "alkynyl" used alone or in combination with other terms in the specification connotes a straight-chain or branched-chain monovalent hydrocarbons with one, two or more double bonds and 2 to 12 carbon atoms. Those having double bonds are preferred. Examples include ethynyl, propynyl, 6-heptynyl, and 7-octynyl. C2 to C6 alkynyl are preferable.

The term "aryl" used alone or in combination with other terms in the specification connotes a monocyclic or condensed-ring aromatic hydrocarbon. Examples include phenyl, 1-naphthyl, 2-naphthyl, and anthryl. Phenyl, 1-naphthyl, and 2-naphthyl are preferable. Phenyl is still more preferable.

Desirable examples of substituents in the "optionally substituted aryls" used in the specification include halogens, alkyls, haloalkyls, and alkoxys.

Desirable examples of substituents in the "optionally substituted aryloxys" used in the specification include halogens, alkyls, haloalkyls, and alkoxys.

Desirable examples of substituents in the "optionally substituted arylthios" used in the specification include halogens, alkyls, haloalkyls, and alkoxys.

The term "mono-substituted sulfinyl" used in the specification connotes a monovalent substituent bound to a sulfinyl. Preferable examples of the substituents in "mono-substituted sulfinyls" include alkyls, haloalkyls, and optionally substituted phenyls. More desirable examples include methyl, trifluoromethyl, phenyl, and 4-chlorophenyl.

The term "mono-substituted sulfonyl" used in the specification connotes a monovalent substituent bound to a sulfonyl. Preferable examples of the substituents in "mono-substituted sulfonyls" include alkyls, haloalkyls, and optionally substituted phenyls. More desirable examples include methyl, trifluoromethyl, phenyl, and 4-chlorophenyl.

Desirable examples of substituents in the "optionally substituted amino carbonyls" used in the specification include alkyls, haloalkyls, and optionally substituted phenyls. More desirable examples include methyl, trifluoromethyl, phenyl, and 4-chlorophenyl.

The term "acyl" used alone or in combination with other terms in the specification connotes an alkyl carbonyl in which the alkyl fraction is aforementioned "alkyl" or an aryl carbonyl in which the aryl fraction is aforementioned "aryl". Examples include acetyl, propionyl, butyryl, and benzoyl.

Desirable examples of substituents in the "optionally substituted acyls" used in the specification include alkyls, haloalkyls, and optionally substituted phenyls. More desirable examples include methyl, trifluoromethyl, phenyl, and 4-chlorophenyl.

Desirable examples of substituents in the "optionally substituted acyloxys" used in the specification include alkyls, haloalkyls, and optionally substituted phenyls. More desirable examples include methyl, trifluoromethyl, phenyl, and 4-chlorophenyl.

The term "halogens" used in the specification connote fluorine, chlorine, bromine, and iodine.

The term "alkoxy" used alone or in combination with other terms in the specification connotes a straight-chain or branched-chain alkyloxy having 1 to 20 carbon atoms. Examples include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy. Desirable examples include methoxy, ethoxy, n-propoxy, and iso-propoxy.

Desirable examples of substituents in the "optionally substituted alkoxys" used in the specification include halogens and aryls. More desirable examples would be fluoros and phenyls.

The "alkylthio" used in the specification include methylthio, ethylthio, n-propylthio, iso-propylthio, n-butylthio, iso-butylthio, sec-butylthio, and tert-butylthio. More desirable examples would be methylthio, ethylthio, n-propylthio, and iso-propylthio.

The term "alkoxy carbonyl" used in the specification connotes methoxy carbonyls, ethoxy carbonyls, and n-propoxy carbonyls.

Desirable examples of substituents in the "optionally substituted alkoxy carbonyls" used in the specification include halogens and aryls. More desirable examples would be fluoros and phenyls.

The term "optionally substituted aminos" used in the specification connote aminos substituted in one or two positions by aforementioned "alkyls", "aralkyls", "acyls", optionally substituted aryl sulfonyls (for example, alkoxy phenyl sulfonyl), aryl alkylene (for example, benzylidene), alkyl sulfonyl, carbamoyl, or unsubstituted aminos. Examples include amino, methyl amino, ethyl amino, dimethyl amino, ethyl methyl amino, diethyl amino, benzyl amino, benzoyl amino, acetyl amino, propionyl amino, tert-butoxy carbonyl amino, benzylidene amino, methyl sulfonyl amino, and 4-methoxy phenyl sulfonyl amino. Amino, methyl amino, dimethyl amino, diethyl amino, and acetyl amino are especially desirable.

Desirable examples of substituents in the "optionally substituted amino carbonyls" used in the specification include alkyls optionally displaced by halogens, and optionally substituted phenyls. More desirable examples include methyl, trifluoromethyl, phenyl, and 4-chlorophenyl.

Desirable examples of substituents in the "optionally substituted alkyls", "optionally substituted alkylthios", "optionally substituted alkoxys", and "optionally substituted alkoxy carbonyls" used in the specification include hydroxys, alkoxys (for example, methoxy, ethoxy), mercapto, alkylthios (for example, methylthio), cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), halogens (for example, fluorine, chlorine, bromine, iodine), carboxys,

alkoxy carbonyls (for example, methoxy carbonyls, ethoxy carbonyls), nitros, cyanos, haloalkyls (for example, trifluoro methyls), optionally substituted aminos (for example, aminos, methyl aminos, dimethyl aminos, carbamoyl aminos, tert-butoxy carbonyl aminos), acyloxys (for example, acetyloxys), optionally substituted aralkoxys (for example, benzyloxys, 4-methoxy phenyl methoxys). One or more of these substituents may be displaced at any position where displacement is permissible.

The preferred number of substituents in "optionally substituted alkyls" would be one to five, preferably one to three. There is no limitation on the site of substituents. Especially desirable examples include halogens, hydroxyls, lower alkoxys, lower alkenyloxys, and acyls.

The term "lower" applied to various types of groups in the specification signifies the number of carbon atoms in the group to be 1 to 10, preferably 1 to 8, more preferably 1 to 6.

Examples of substituents in the "optionally substituted alkenyls", "optionally substituted alkenyloxys", "optionally substituted alkynyls", and "optionally substituted alkynyloxys" in the specification include hydroxy, alkoxy (for example, methoxy, ethoxy), mercapto, alkylthios (for example, methylthio), cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), halogens (for example, fluorine, chlorine, bromine, iodine), carboxys, alkoxy carbonyls (for example, methoxy carbonyls, ethoxy carbonyls), nitros, cyanos, haloalkyls (for example, trifluoro methyls), optionally substituted aminos (for example, aminos, methyl aminos, dimethyl aminos, carbamoyl aminos, tert-butoxy carbonyl aminos), acyloxys (for example, acetyloxys), optionally substituted aralkoxys (for example, benzyloxys, 4-methoxy phenyl methoxys), overseas aryls (for example, phenyl). One or more of these substituents may be displaced at any position where displacement is permissible.

The preferred number of substituents in "optionally substituted alkenyls" and "optionally substituted alkynyls" would be one to five, preferably one to three. There is no limitation on the site of substituents. Desirable examples of aforementioned substituents include halogens, hydroxyls, lower alkoxys, lower alkenyloxys, and acyls.

"Optionally substituted alkyls" connotes straight-chain or branched-chain C1 to C20 alkyls. Examples include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl, tert-butyl, n-pentyl, 1-ethyl propyl, 2-methyl butyl, 3-methyl butyl, 2,2-dimethyl propyl, n-hexyl, 2-methyl pentyl, 3-methyl pentyl, 4-methyl pentyl, n-heptyl, 2-methyl hydroxy, 3-methyl hexyl, 4-methyl hexyl, 5-methyl hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, tetrahydrogeranyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-octadecyl, n-nonadecyl, and n-eicosanyl. Methyl, ethyl, n-propyl, isopropyl, n-butyl, trifluouromethyl, 2,2,2-trifluoro ethyl, hydroxy methyl, cyclohexyl methyl, carboxy ethyl, acetyloxy ethyl, benzyloxy methyl would be preferable. C1 to C10 alkyls would be especially desirable. C1 to C6 alkyls would be even more desirable.

Especially desirable examples of "optionally substituted alkyls" include methyl, ethyl, n-propyl, isopropyl, n-butyl, trifluoro methyl, 2,2,2-trifluoroethyl, hydroxymethyl, cyclohexyl methyl,

carboxy ethyl, acetyloxy ethyl, benzyloxy methyl. Among these, methyl, ethyl, n-propyl, isopropyl, n-butyl, trifluoro methyl, 2,2,2-trifluoro ethyl would be preferable.

The "optionally substituted alkenyls" in the specification connote straight-chain or branched-chain C2 to C12 alkenyls. These can have the permissible number of double bonds at the permissible positions. Their arrangement in double bonds may be the (E) arrangement or the (Z) arrangement, and permissible examples include vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1- pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl, geranyl, 1-decenyl, 1-tetradecenyl, 1-octadecenyl, 9-octadecenyl, 1-eicosenyl, 3,7,11,15-tetramethyl-1-hexadecenyl. C2 to C8 alkenyls are preferable. C2 to C6 alkenyls would be especially preferable. Among these, vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-methyl-2-butenyl would be especially preferable.

The "optionally substituted alkynyl" in the specification connote straight-chain or branched-chain C2 to C12 alkynyls. These can have the permissible number of double bonds at the permissible positions, and permissible examples include alkynyls having 2 to 20 carbon atoms optionally having double bonds such as ethynyl, 1-propynyl, 2-propynyl (propargyl), 2-butynyl, 2-pentene-4-ynyl. C2 to C8 alkynyls would be preferable. C2 to C6 alkynyls would be still more preferable.

"Optionally substituted acyls" connotes acyls derived from optionally substituted carboxylic acid, optionally substituted oxycarboxylic acid, optionally substituted sulfonic acid, or optionally substituted sulfinic acid. Concrete examples are groups represented by the following formula

$$R^9C(O)-,\ R^{10}OC(O)-,\ R^{11}S(O)_2-,\ R^{12}S(O)-$$

[In the formula, R^9, R^{10}, R^{11}, and R^{12}, respectively, represent optionally substituted hydrocarbons or heterocyclic rings]. The group represented by the formula $R^9C(O)-$ would be preferable.

The "hydrocarbons" in the "optionally substituted hydrocarbons or heterocyclic rings" represented by R^9, R^{10}, R^{11}, and R^{12} are straight-chain or branched aliphatic hydrocarbons as acyclic groups (alkyls, alkenyls, alkynyls, etc.) while cyclic groups would be saturated or unsaturated alicyclic hydrocarbons (cycloalkyls, cycloalkenyls, cycloalkadienyls, etc.), monocyclic or condensed polycyclic aryls.

Examples of alkyls, alkenyls, and alkynyls of aforementioned "hydrocarbons" are similar to aforementioned alkyls, alkenyls, and alkynyls.

Desirable concrete examples of substituents in "optionally substituted acyls" include halogens, hydroxyls, substituted or unsubstituted lower alkoxys, substituted or unsubstituted lower alkenyloxys, substituted or unsubstituted lower alkyl carbonyloxys, carboxys, substituted or unsubstituted carbamoyls, cyanos, substituted or unsubstituted aminos, substituted or unsubstituted amidinos, azides, nitros, nitrosos, mercaptos, substituted or unsubstituted lower alkylthios, sulfos, substituted or unsubstituted saturated or unsaturated alicyclic hydrocarbons,

substituted or unsubstituted monocyclic or condensed polycyclic aryls, substituted or unsubstituted heterocyclic rings, and substituted or unsubstituted acyls.

The number of substituents in "optionally substituted acyls" should be 1 to 5, preferably 1 to 3. There is no limitation on the substituent position. Desirable substituents among the aforementioned are halogens, hydroxyls, lower alkoxys, lower alkenyloxys and acyls.

Desirable examples of "optionally substituted acyls" are optionally substituted acetyls and optionally substituted benzoyls. Examples of substituents that displace benzene-ring hydrogens in benzoyls and of substitution positions include 2-, 3-, and 4-fluoro; 2-, 3-, and 4-chloro; 2-, 3-, and 4-bromo; 2-, 3-, and 4-iodo; 2-, 3-, 4-methyl; 2,3-, 2,4-, and 2,5-dimethyl; 2,6-, 3,4-, and 3,5-dimethyl; 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, 3,4,5-trimethyl; 2-, 3-, and 4-ethyl; 2-, 3-, and 4-ethyl; 2-, 3-, and 4-propyl, 2-, 3-, and 4-trifluoromethyl; 2-, 3-, and 4-methoxy; 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, and 3,5-dimethoxy, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, and 3,4,5-trimethoxy; 2-, 3-, and 4-ethoxy; 2-, 3-, and 4-propoxy; 2-, 3-, and 4-trifluoromethoxy; 2-, 3-, and 4-cyano; 2-, 3-, and 4-nitro; as well as arbitrary permissible combinations of these substituents and substitution positions.

The term "tri-substituted silyl" used alone or in combination with other terms in the specification connotes silyls ($-SiH_3$) in which three hydrogens are displaced. Preferable examples of tri-substituted silyls include optionally substituted trialkyl silyls, dialkyl monoaryl silyls, and monoalkyl diaryl silyls. Concrete examples of trialkyl silyls include trimethyl silyls, triethyl silyls, and tert-butyl dimethyl silyls. An example of monoalkyl diaryl silyls is tert-butyl diphenyl silyl.

Desirable examples of substituents in "optionally substituted tri-substituted silyloxys" include halogens and alkoxys.

The statement "Xm in formula (E)" or "Xm in formula (I-E)" in the specification specifies the substitution position of Xm in accordance with nomenclature rules for substitution positions on benzene rings stated in formula (I-E) in the specification.

"The name for each substitution position conforms to the nomenclature for substitution positions in general formula (I-A)" means that the substitution position of Xm is specified in accordance with the notational conventions for positions on the benzene ring stated in formula (I-A) in the specification. For example, "4-chloro that conforms to the nomenclature for substitution positions in general formula (I-A)" corresponds to 6-chloro based on the nomenclature for substitution positions in general formula (I-E) in the specification, and to 5-chloro based on the nomenclature for substitution positions in general formula (I-F) in the specification.

Various types of stereoisomers of the compound pursuant to the present invention can be derived, and each of them is included among the compounds pursuant to the present invention.

For example, the "notation (*)" in the formula of the compound stated in the specification represents asymmetric carbons, and R forms, S forms or mixed forms of stereoisomers may be denoted. However, the compound of formula (I-E) preferably would be a stereoisomers in which position 3 of 2-H-1-benzopyran is the R arrangement.

In addition, geometrical isomers may be cis or trans form.

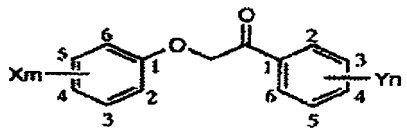
The compounds used in the present invention preferably are compounds represented by the following compound numbers stated in the table or working examples.

A-47, A-56 Working (Example 1), A-66,
B-9, B-13, B-49, B-51, B-58 (Working Example 2),
B-62, B-70,
C-13, C-15 (Working Example 3), C-19,
D-13 (Working Example 4),
E-10, E-11, E-13 (Working Example 9), E-14, E-22,
E-24, E-37, E-55, E-75, E-76 (Working Example 5),
E-77, E-78, E-83, E-84, E-86, E-87,
E-90, E-93, E-94,
F-21, F-22, F-23, F-35 (Working Example 6), F-38,
F-39, F-40,
H-11 (Working Example 7) , H-18, H-29,
J-8, J-10, J-11, J-14, J-15, J-16 (Working Example 8),
J-39, J-41, J-44, J-47,
K-27, K-28. K-30, K-31, K-36, K-37 (Working Example 10),
K-38, K-39, K-41, K-42, K-43,
K-50, K-53, K-57, K-58, K-59, K-90,
K-91, K-92.

Compounds stated in each working example are especially desirable.

The compounds represented by general formula (I) and their uses such as for immunopotentiation are novel, and desirable examples include compounds in which the individual substituents are combinations of any from Tables 1 to 11 presented below. The "No." column among the notations in the table denotes the compound number. In addition, H denotes hydrogen, OH denotes hydroxyl, Me denotes methyl, Et denotes ethyl, i-Pr denotes isopropyl, TBS denotes tert-butyl dimethyl silyl, SEM denotes 2-(trimethyl silyl) ethoxymethyl. Bzl denotes benzyl, Me denotes methyl, Ph denotes phenyl, MOM denotes methoxymethyl, TMS denotes trimethyl silyl, prenyl denotes prenyl (specifically, 3-methyl-2-butenyl), prenyloxy denotes prenyloxy, "OC_6H_{11}-C" denotes cyclohexyl oxy, "OC_6H_{11}-n" denotes straight-chain hexyloxy, Ts denotes p-toluenesulfonyl, TBDPS denotes tert-butyl diphenyl silyl, Bu^t denotes tert-butyl, ^iPr denotes isopropyl, picolyloxy denotes picolyloxy. In addition, "$(\ )_2$" denotes a double bond. For example, "5,6-$(OMe)_2$" denotes "5,6-dimethoxy".

(Table 1)



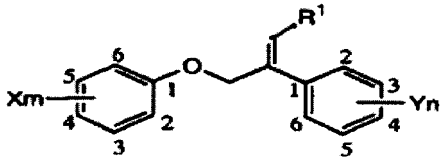
(1-A)

No.	Xm	Yn
A-1	2-OH	2,4-$(OBzl)_2$
A-2	3-OH	2,4-$(OBzl)_2$
A-3	4-OH	2,4-$(OBzl)_2$
A-4	2-OMe	2-Ph
A-5	2-OMe	2,4-$(OMe)_2$
A-6	2-OMe	2,4-$(OBzl)_2$
A-7	3-OMe	2-Ph
A-8	3-OMe	2,4-$(OMe)_2$
A-9	3-OMe	2,4-$(OBzl)_2$
A-10	4-OMe	2-Ph
A-11	4-OMe	2,4-$(OMe)_2$
A-12	4-OMe	2,4-$(OBzl)_2$
A-13	2-OBzl	2-Ph
A-14	2-OBzl	2,4-$(OMe)_2$
A-15	2-OBzl	2,4-$(OBzl)_2$
A-16	3-OBzl	2-Ph
A-17	3-OBzl	2,4-$(OMe)_2$
A-18	3-OBzl	2,4-$(OBzl)_2$
A-19	4-OBzl	2-Ph
A-20	4-OBzl	2,4-$(OMe)_2$
A-21	4-OBzl	2,4-$(OBzl)_2$
A-22	3,5-$(OH)_2$	2-Ph
A-23	3,5-$(OH)_2$	2,4-$(OMe)_2$
A-24	3,5-$(OH)_2$	2,4-$(OBzl)_2$
A-25	3-OH-5-OBzl	2,4-$(OBzl)_2$
A-26	3-OH-5-OTMS	2,4-$(OBzl)_2$
A-27	2,3-$(OMe)_2$	2-Ph
A-28	2,3-$(OMe)_2$	2,4-$(OBzl)_2$
A-29	2,3-$(OMe)_2$	2,4-$(OMOM)_2$
A-30	2,3-$(OMe)_2$	2,4-$(OTBS)_2$
A-31	2,4-$(OMe)_2$	2-Ph
A-32	2,4-$(OMe)_2$	2,4-$(OBzl)_2$
A-33	2,4-$(OMe)_2$	2,4-$(OMOM)_2$
A-34	2,4-$(OMe)_2$	2,4-$(OTBS)_2$
A-35	2,5-$(OMe)_2$	2-Ph

(Table 1 continued)

A-36	2,5-$(OMe)_2$	2,4-$(OBzl)_2$
A-37	2,5-$(OMe)_2$	2,4-$(OMOM)_2$
A-38	2,5-$(OMe)_2$	2,4-$(OTBS)_2$
A-39	2,6-$(OMe)_2$	2-Ph
A-40	2,6-$(OMe)_2$	2,4-$(OBzl)_2$
A-41	2,6-$(OMe)_2$	2,4-$(OMOM)_2$
A-42	2,6-$(OMe)_2$	2,4-$(OTBS)_2$
A-43	3,4-$(OMe)_2$	2-Ph
A-44	3,4-$(OMe)_2$	2,4-$(OBzl)_2$
A-45	3,4-$(OMe)_2$	2,4-$(OMOM)_2$
A-46	3,4-$(OMe)_2$	2,4-$(OTBS)_2$
A-47	3,5-$(OMe)_2$	2-Ph
A-48	3,5-$(OMe)_2$	3-Ph
A-49	3,5-$(OMe)_2$	4-Ph
A-50	3,5-$(OMe)_2$	2-OH
A-51	3,5-$(OMe)_2$	3-OH
A-52	3,5-$(OMe)_2$	4-OH
A-53	3,5-$(OMe)_2$	2-OMe
A-54	3,5-$(OMe)_2$	3-OMe
A-55	3,5-$(OMe)_2$	4-Ome
A-56	3,5-$(OMe)_2$	2-OBzl
A-57	3,5-$(OMe)_2$	3-OBzl
A-58	3,5-$(OMe)_2$	4-OBzl
A-59	3,5-$(OMe)_2$	2,4-Me_2
A-60	3,5-$(OMe)_2$	2,4-$(OH)_2$
A-61	3,5-$(OMe)_2$	2-OH-4-OBzl
A-62	3,5-$(OMe)_2$	2-OBzl-4-OH
A-63	3,5-$(OMe)_2$	2,4-$(OMe)_2$
A-64	3,5-$(OMe)_2$	2-OMe-4-OBzl
A-65	3,5-$(OMe)_2$	2-OBzl-4-OMe
A-66	3,5-$(OMe)_2$	2,4-$(OBzl)_2$
A-67	3,5-$(OMe)_2$	2,4-$(OMOM)_2$
A-68	3,5-$(OMe)_2$	2,4-$(OTBS)_2$
A-69	3,5-$(OMe)_2$	2,4-$(OSEM)_2$
A-70	3,5-$(OBzl)_2$	2,4-$(OBzl)_2$
A-71	3,5-$(OMOM)_2$	2,4-$(OBzl)_2$
A-72	3,5-$(OTBS)_2$	2,4-$(OBzl)_2$
A-73	3,5-$(OMe)_2$-4-prenyl	2,4-$(OH)_2$
A-74	3,5-$(OMe)_2$-4-prenyl	2,4-$(OSEM)_2$
A-75	3,5-$(OMe)_2$-4-prenyl	2-OH-4-OSEM

(Table 2)



(I-B)

No.	Xm	Yn	R^1
B-1	2-OH	2,4-$(OBzl)_2$	H
B-2	3-OH	2,4-$(OBzl)_2$	H
B-3	4-OH	2,4-$(OBzl)_2$	H
B-4	2-OMe	2-Ph	H
B-5	2-OMe	2,4-$(OMe)_2$	H
B-6	2-OMe	2,4-$(OBzl)_2$	H
B-7	3-OMe	2-Ph	H
B-8	3-OMe	2,4-$(OMe)_2$	H
B-9	3-OMe	2,4-$(OBzl)_2$	H
B-10	3-OMe	2,4-$(OBzl)_2$	Me
B-11	4-OMe	2-Ph	H
B-12	4-OMe	2,4-$(OMe)_2$	H
B-13	4-OMe	2,4-$(OBzl)_2$	H
B-14	2-OBzl	2-Ph	H
B-15	2-OBzl	2,4-$(OMe)_2$	H
B-16	2-OBzl	2,4-$(OBzl)_2$	H
B-17	3-OBzl	2-Ph	H
B-18	3-OBzl	2,4-$(OMe)_2$	H
B-19	3-OBzl	2,4-$(OBzl)_2$	H
B-20	4-OBzl	2-Ph	H
B-21	4-OBzl	2,4-$(OMe)_2$	H
B-22	4-OBzl	2,4-$(OBzl)_2$	H
B-23	3,5-$(OH)_2$	2-Ph	H
B-24	3,5-$(OH)_2$	2,4-$(OMe)_2$	H
B-25	3,5-$(OH)_2$	2,4-$(OBzl)_2$	H
B-26	3-OH-5-OBzl	2,4-$(OBzl)_2$	H
B-27	3-OH-5-OTMS	2,4-$(OBzl)_2$	H
B-28	2,3-$(OMe)_2$	2-Ph	H
B-29	2,3-$(OMe)_2$	2,4-$(OBzl)_2$	H
B-30	2,3-$(OMe)_2$	2,4-$(OMOM)_2$	H
B-31	2,3-$(OMe)_2$	2,4-$(OTBS)_2$	H
B-32	2,4-$(OMe)_2$	2-Ph	H
B-33	2,4-$(OMe)_2$	2,4-$(OBzl)_2$	H
B-34	2,4-$(OMe)_2$	2,4-$(OMOM)_2$	H
B-35	2,4-$(OMe)_2$	2,4-$(OTBS)_2$	H

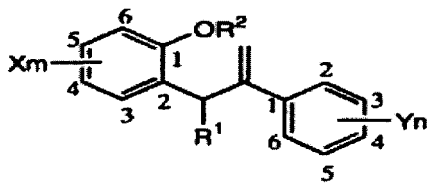
(Table 2 continued)

B-36	2,5-$(OMe)_2$	2-Ph	H
B-37	2,5-$(OMe)_2$	2,4-$(OBzl)_2$	H
B-38	2,5-$(OMe)_2$	2,4-$(OMOM)_2$	H
B-39	2,5-$(OMe)_2$	2,4-$(OTBS)_2$	H
B-40	2,6-$(OMe)_2$	2-Ph	H
B-41	2,6-$(OMe)_2$	2,4-$(OBzl)_2$	H
B-42	2,6-$(OMe)_2$	2,4-$(OMOM)_2$	H
B-43	2,6-$(OMe)_2$	2,4-$(OTBS)_2$	H
B-44	3,4-$(OMe)_2$	2-Ph	H
B-45	3,4-$(OMe)_2$	2,4-$(OBzl)_2$	H
B-46	3,4-$(OMe)_2$	2,4-$(OMOM)_2$	H
B-47	3,4-$(OMe)_2$	2,4-$(OTBS)_2$	H
B-48	3,5-$(OMe)_2$	H	H
B-49	3,5-$(OMe)_2$	2-Ph	H
B-50	3,5-$(OMe)_2$	3-Ph	H
B-51	3,5-$(OMe)_2$	4-Ph	H
B-52	3,5-$(OMe)_2$	2-OH	H
B-53	3,5-$(OMe)_2$	3-OH	H
B-54	3,5-$(OMe)_2$	4-OH	H
B-55	3,5-$(OMe)_2$	2-OMe	H
B-56	3,5-$(OMe)_2$	3-OMe	H
B-57	3,5-$(OMe)_2$	4-OMe	H
B-58	3,5-$(OMe)_2$	2-OBzl	H
B-59	3,5-$(OMe)_2$	2-OBzl	Me
B-60	3,5-$(OMe)_2$	3-OBzl	H
B-61	3,5-$(OMe)_2$	4-OBzl	H
B-62	3,5-$(OMe)_2$	2,4-Me_2	H
B-63	3,5-$(OMe)_2$	2,4-Me_2	Me
B-64	3,5-$(OMe)_2$	2,4-$(OH)_2$	H
B-65	3,5-$(OMe)_2$	2-OH-4-OBzl	H
B-66	3,5-$(OMe)_2$	2-OBzl-4-OH	H
B-67	3,5-$(OMe)_2$	2,4-$(OMe)_2$	H
B-68	3,5-$(OMe)_2$	2-OMe-4-OBzl	H
B-69	3,5-$(OMe)_2$	2-OBzl-4-OMe	H
B-70	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	H
B-71	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	Me
B-72	3,5-$(OMe)_2$	2,4-$(OMOM)_2$	H
B-73	3,5-$(OMe)_2$	2,4-$(OTBS)_2$	H
B-74	3,5-$(OMe)_2$	2,4-$(OSEM)_2$	H
B-75	3,5-$(OBzl)_2$	2,4-$(OBzl)_2$	H

(Table 2 continued)

B-76	3,5-$(OMOM)_2$	2,4-$(OBzl)_2$	H
B-77	3,5-$(OTBS)_2$	2,4-$(OBzl)_2$	H
B-78	3,5-$(OMe)_2$-4-prenyl	2,4-$(OH)_2$	H
B-79	3,5-$(OMe)_2$-4-prenyl	2,4-$(OSEM)_2$	H
B-80	3,5-$(OMe)_2$-4-prenyl	2-OH-4-OSEM	H

(Table 3)



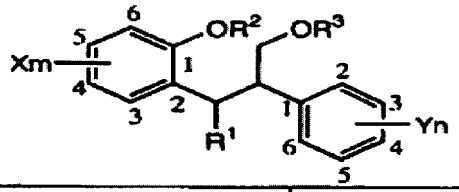
(I-C)

No.	Xm	Yn	R^1	R^2
C-1	3-OMe	2,4-$(OMe)_2$	H	COMe
C-2	3-OMe	2,4-$(OBzl)_2$	H	COMe
C-3	4-OMe	2,4-$(OBzl)_2$	H	COMe
C-4	5-OMe	2,4-$(OMe)_2$	H	COMe
C-5	5-OMe	2,4-$(OBzl)_2$	H	COMe
C-6	6-OMe	2,4-$(OBzl)_2$	H	COMe
C-7	3,4-$(OMe)_2$	4-Ph	H	COMe
C-8	3,4-$(OMe)_2$	2,4-$(OH)_2$	H	COMe
C-9	3,4-$(OMe)_2$	2,4-$(OMe)_2$	H	COMe
C-10	3,4-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe
C-11	3,5-$(OMe)_2$	2-Ph	H	COMe
C-12	3,5-$(OMe)_2$	4-Ph	H	H
C-13	3,5-$(OMe)_2$	4-Ph	H	COMe
C-14	3,5-$(OMe)_2$	4-Ph	Me	COMe
C-15	3,5-$(OMe)_2$	2-OBzl	H	COMe
C-16	3,5-$(OMe)_2$	3-OBzl	H	COMe
C-17	3,5-$(OMe)_2$	4-OBzl	H	COMe
C-18	3,5-$(OMe)_2$	2,4-Me_2	H	H
C-19	3,5-$(OMe)_2$	2,4-Me_2	H	COMe
C-20	3,5-$(OMe)_2$	2,4-Me_2	Me	COMe
C-21	3,5-$(OMe)_2$	2,4-$(OH)_2$	H	COMe
C-22	3,5-$(OMe)_2$	2,4-$(OMe)_2$	H	COMe
C-23	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	H	H
C-24	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe
C-25	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	Me	COMe
C-26	3,6-$(OMe)_2$	4-Ph	H	COMe
C-27	3,6-$(OMe)_2$	2,4-$(OH)_2$	H	COMe
C-28	3,6-$(OMe)_2$	2,4-$(OMe)_2$	H	COMe
C-29	3,6-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe
C-30	4,5-$(OMe)_2$	4-Ph	H	COMe

(Table 3 continued)

C-31	4,5-$(OMe)_2$	2,4-$(OH)_2$	H	COMe
C-32	4,5-$(OMe)_2$	2,4-$(OMe)_2$	H	COMe
C-33	4,5-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe
C-34	5,6-$(OMe)_2$	4-Ph	H	COMe
C-35	5,6-$(OMe)_2$	2,4-$(OH)_2$	H	COMe
C-36	5,6-$(OMe)_2$	2,4-$(OMe)_2$	H	COMe
C-37	5,6-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe
C-38	3,5-$(OMe)_2$-4-Me	2-OMe	H	COMe
C-39	3,5-$(OMe)_2$-4-Me	3-OMe	H	COMe
C-40	3,5-$(OMe)_2$-4-Me	4-OMe	H	COMe
C-41	3,5-$(OMe)_2$-4-Me	2-OBzl	H	COMe
C-42	3,5-$(OMe)_2$-4-Me	3-OBzl	H	COMe
C-43	3,5-$(OMe)_2$-4-Me	4-OBzl	H	COMe
C-44	3,5-$(OMe)_2$-4-Me	2,4-Me_2	H	COMe
C-45	3,5-$(OMe)_2$-4-Me	2,4-$(OH)_2$	H	COMe
C-46	3,5-$(OMe)_2$-4-Me	2,4-$(OMe)_2$	H	COMe
C-47	3,5-$(OMe)_2$-4-Me	2,4-$(OBzl)_2$	H	H
C-48	3,5-$(OMe)_2$-4-Me	2,4-$(OBzl)_2$	H	COMe
C-49	3,5-$(OMe)_2$-4-prenyl	2-OMe	H	COMe
C-50	3,5-$(OMe)_2$-4-prenyl	3-OMe	H	COMe
C-51	3,5-$(OMe)_2$-4-prenyl	4-OMe	H	COMe
C-52	3,5-$(OMe)_2$-4-prenyl	2-OBzl	H	COMe
C-53	3,5-$(OMe)_2$-4-prenyl	3-OBzl	H	COMe
C-54	3,5-$(OMe)_2$-4-prenyl	4-OBzl	H	COMe
C-55	3,5-$(OMe)_2$-4-prenyl	2,4-Me_2	H	COMe
C-56	3,5-$(OMe)_2$-4-prenyl	2,4-$(OH)_2$	H	COMe
C-57	3,5-$(OMe)_2$-4-prenyl	2,4-$(OMe)_2$	H	COMe
C-58	3,5-$(OMe)_2$-4-prenyl	2,4-$(OBzl)_2$	H	H
C-59	3,5-$(OMe)_2$-4-prenyl	2,4-$(OBzl)_2$	H	COMe
C-60	3,5-$(OMe)_2$-4-prenyl	2,4-$(OBzl)_2$	Me	COMe

(Table 4)



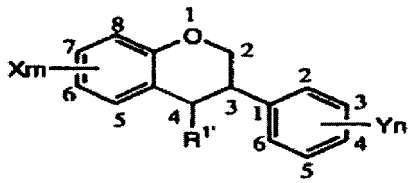
(I-D)

No.	Xm	Yn	R^1	R^2	R^3
D-1	3-OMe	2,4-$(OMe)_2$	H	H	H
D-2	3-OMe	2,4-$(OBzl)_2$	H	H	H
D-3	4-OMe	2,4-$(OBzl)_2$	H	H	H
D-4	5-OMe	2,4-$(OMe)_2$	H	H	H
D-5	5-OMe	2,4-$(OBzl)_2$	H	H	H
D-6	6-OMe	2,4-$(OBzl)_2$	H	H	H
D-7	3,4-$(OMe)_2$	4-Ph	H	H	H
D-8	3,4-$(OMe)_2$	2,4-$(OH)_2$	H	H	H
D-9	3,4-$(OMe)_2$	2,4-$(OMe)_2$	H	H	H
D-10	3,4-$(OMe)_2$	2,4-$(OBzl)_2$	H	H	H
D-11	3,5-$(OMe)_2$	2-Ph	H	H	H
D-12	3,5-$(OMe)_2$	4-Ph	H	H	H
D-13	3,5-$(OMe)_2$	2-OBzl	H	H	H
D-14	3,5-$(OMe)_2$	3-OBzl	H	H	H
D-15	3,5-$(OMe)_2$	4-OBzl	H	H	H
D-16	3,5-$(OMe)_2$	2,4-Me_2	H	H	H
D-17	3,5-$(OMe)_2$	2,4-$(OH)_2$	H	H	H
D-18	3,5-$(OMe)_2$	2,4-$(OMe)_2$	H	H	H
D-19	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	H	H	H
D-20	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe	H
D-21	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	Me	H	H
D-22	3,6-$(OMe)_2$	4-Ph	H	H	H
D-23	3,6-$(OMe)_2$	2,4-$(OH)_2$	H	H	H
D-24	3,6-$(OMe)_2$	2,4-$(OMe)_2$	H	H	H
D-25	3,6-$(OMe)_2$	2,4-$(OBzl)_2$	H	H	H
D-26	4,5-$(OMe)_2$	4-Ph	H	H	H
D-27	4,5-$(OMe)_2$	2,4-$(OH)_2$	H	H	H
D-28	4,5-$(OMe)_2$	2,4-$(OMe)_2$	H	H	H
D-29	4,5-$(OMe)_2$	2,4-$(OBzl)_2$	H	H	H
D-30	5,6-$(OMe)_2$	4-Ph	H	H	H

(Table 4 continued)

D-31	5,6-$(OMe)_2$	2,4-$(OH)_2$	H	H	H
D-32	5,6-$(OMe)_2$	2,4-$(OMe)_2$	H	H	H
D-33	5,6-$(OMe)_2$	2,4-$(OBzl)_2$	H	H	H
D-34	3,5-$(OMe)_2$-4-Me	2-OMe	H	H	H
D-35	3,5-$(OMe)_2$-4-Me	3-OMe	H	H	H
D-36	3,5-$(OMe)_2$-4-Me	4-OMe	H	H	H
D-37	3,5-$(OMe)_2$-4-Me	2-OBzl	H	H	H
D-38	3,5-$(OMe)_2$-4-Me	3-OBzl	H	H	H
D-39	3,5-$(OMe)_2$-4-Me	4-OBzl	H	H	H
D-40	3,5-$(OMe)_2$-4-Me	2,4-Me_2	H	H	H
D-41	3,5-$(OMe)_2$-4-Me	2,4-$(OH)_2$	H	H	H
D-42	3,5-$(OMe)_2$-4-Me	2,4-$(OMe)_2$	H	H	H
D-43	3,5-$(OMe)_2$-4-Me	2,4-$(OBzl)_2$	H	H	H
D-44	3,5-$(OMe)_2$-4-Me	2,4-$(OBzl)_2$	H	H	H
D-45	3,5-$(OMe)_2$-4-Me	2,4-$(OBzl)_2$	Me	H	H
D-46	3,5-$(OMe)_2$-4-prenyl	2-OMe	H	COMe	H
D-47	3,5-$(OMe)_2$-4-prenyl	3-OMe	H	H	H
D-48	3,5-$(OMe)_2$-4-prenyl	4-OMe	H	H	H
D-49	3,5-$(OMe)_2$-4-prenyl	2-OBzl	H	H	H
D-50	3,5-$(OMe)_2$-4-prenyl	3-OBzl	H	H	H
D-51	3,5-$(OMe)_2$-4-prenyl	4-OBzl	H	H	H
D-52	3,5-$(OMe)_2$-4-prenyl	2,4-Me_2	H	H	H
D-53	3,5-$(OMe)_2$-4-prenyl	2,4-$(OH)_2$	H	H	H
D-54	3,5-$(OMe)_2$-4-prenyl	2,4-$(OMe)_2$	H	H	H
D-55	3,5-$(OMe)_2$-4-prenyl	2,4-$(OBzl)_2$	H	H	H
D-56	3,5-$(OMe)_2$-4-prenyl	2,4-$(OBzl)_2$	H	COMe	H
D-57	3,5-$(OMe)_2$-4-prenyl	2,4-$(OBzl)_2$	Me	H	H

Table 5



(I-E)

No.	Xm	Yn	R1'
E-1	H	H	H
E-2	H	3-NO_2	H
E-3	H	4-F	H
E-4	H	4-CH_3	H
E-5	H	4-CO_2H	H
E-6	6-Cl	H	H
E-7	6-Cl	3-NO_2	H
E-8	6-Cl	4-F	H
E-9	6-Cl	4-CH_3	H
E-10	5-OMe	H	H
E-11	5-OMe	4-F	H
E-12	5-OMe	4-F	Me
E-13	5-OMe	4-Me	H
E-14	5-OMe	2-OBzl	H
E-15	5-OMe	3-OBzl	H
E-16	5-OMe	4-OBzl	H
E-17	5-OMe	2-CF_3	H
E-18	5-OMe	2-CF_3	H
E-19	5-OMe	4-CO_2H	H
E-20	5-OMe	3-NH_2	H
E-21	5-OMe	3-NO_2	H
E-22	5-OMe	2,4-$(OH)_2$	H
E-23	5-OMe	2,4-$(OMe)_2$	H
E-24	5-OMe	2,4-$(OBzl)_2$	H
E-25	5-OMe	2,4-$(OBzl)_2$	Me
E-26	6-OMe	H	H
E-27	6-OMe	4-F	H
E-28	6-OMe	4-Me	H
E-29	6-OMe	2-OBzl	H
E-30	6-OMe	3-OBzl	H
E-31	6-OMe	4-OBzl	H
E-32	6-OMe	2-CF_3	H
E-33	6-OMe	2-CF_3	H
E-34	6-OMe	4-CO_2H	H
E-35	6-OMe	3-NH_2	H

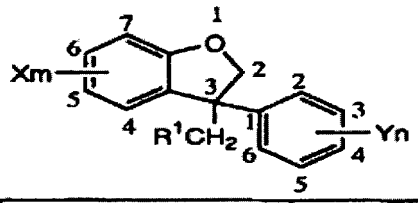
(Table 5 continued)

E-36	6-OMe	3-NO_2	H
E-37	6-OMe	2,4-$(OH)_2$	H
E-38	6-OMe	2,4-$(OMe)_2$	H
E-39	6-OMe	2,4-$(OBzl)_2$	H
E-40	6-OMe	2,4-$(OBzl)_2$	Me
E-41	7-OMe	H	H
E-42	7-OMe	4-F	H
E-43	7-OMe	4-Me	H
E-44	7-OMe	2-OBzl	H
E-45	7-OMe	2-OBzl	Me
E-46	7-OMe	3-OBzl	H
E-47	7-OMe	4-OBzl	H
E-48	7-OMe	2-CF_3	H
E-49	7-OMe	2-CF_3	H
E-50	7-OMe	4-CO_2H	H
E-51	7-OMe	3-NH_2	H
E-52	7-OMe	3-NO_2	H
E-53	7-OMe	2,4-$(OBzl)_2$	H
E-54	7-OMe	2,4-$(OBzl)_2$	Me
E-55	7-OMe	2,4-$(OH)_2$	H
E-56	7-OMe	2,4-$(OMe)_2$	H
E-57	7-OMe	2,4-$(OMe)_2$	Me
E-58	8-OMe	H	H
E-59	8-OMe	2-CF_3	H
E-60	8-OMe	3-NH_2	H
E-61	8-OMe	4-Me	H
E-62	8-OMe	4-CO_2H	H
E-63	8-OMe	4-F	H
E-64	8-OMe	2-OBzl	H
E-65	8-OMe	2-OBzl	Me
E-66	8-OMe	3-OBzl	H
E-67	8-OMe	4-OBzl	H
E-68	8-OMe	2,4-$(OBzl)_2$	H
E-69	8-OMe	2,4-$(OH)_2$	H
E-70	8-OMe	2,4-$(OMe)_2$	H
E-71	5,6-$(OMe)_2$	H	H
E-72	5,6-$(OMe)_2$	2-OBzl	H
E-73	5,6-$(OMe)_2$	3-OBzl	H
E-74	5,6-$(OMe)_2$	4-OBzl	H
E-75	5,7-$(OMe)_2$	H	H

(Table 5 continued)

E-76	5,7-$(OMe)_2$	2-OBzl	H
E-77	5,7-$(OMe)_2$	3-OBzl	H
E-78	5,7-$(OMe)_2$	4-OBzl	H
E-79	5,7-$(OMe)_2$	2-OMs	H
E-80	5,7-$(OMe)_2$	2-OC_6H_{11}-c	H
E-81	5,7-$(OMe)_2$	2-OTBDPS	H
E-82	5,7-$(OMe)_2$	2-OCH_2=$CHCH_2$	H
E-83	5,7-$(OMe)_2$	2-$OCH_2CH_2(OCH_2-)_2$	H
E-84	5,7-$(OMe)_2$	2-prenyloxy	H
E-85	5,7-$(OMe)_2$	2-OTs	H
E-86	5,7-$(OMe)_2$	2-OC_6H_{11}-n	H
E-87	5,7-$(OMe)_2$	2-OCH_2CH_2OPh	H
E-88	5,7-$(OMe)_2$	2-(Z)-OCH_2=$CHCH_2CO_2Et$	H
E-89	5,7-$(OMe)_2$	2-$OCH_2CH_2CH_2CN$	H
E-90	5,7-$(OMe)_2$	2-OH	H
E-91	5,7-$(OMe)_2$	3-OH	H
E-92	5,7-$(OMe)_2$	4-OH	H
E-93	5,7-$(OMe)_2$	2,4-Me_2	H
E-94	5,7-$(OMe)_2$	4-Ph	H
E-95	5,7-$(OMe)_2$	2-Ph	H
E-96	5,7-$(OMe)_2$-6-Me	H	H
E-97	5,7-$(OMe)_2$-6-Me	2-OBzl	H
E-98	5,7-$(OMe)_2$-6-Me	3-OBzl	H
E-99	5,7-$(OMe)_2$-6-Me	4-OBzl	H
E-100	5,7-$(OMe)_2$-6-prenyl	H	H
E-101	5,7-$(OMe)_2$-6-prenyl	2-OBzl	H
E-102	5,7-$(OMe)_2$-6-prenyl	3-OBzl	H
E-103	5,7-$(OMe)_2$-6-prenyl	4-OBzl	H
E-104	5,8-$(OMe)_2$	H	H
E-105	5,8-$(OMe)_2$	2-OBzl	H
E-106	5,8-$(OMe)_2$	3-OBzl	H
E-107	5,8-$(OMe)_2$	4-OBzl	H
E-108	6,7-$(OMe)_2$	H	H
E-109	6,7-$(OMe)_2$	2-OBzl	H
E-110	6,7-$(OMe)_2$	3-OBzl	H
E-111	6,7-$(OMe)_2$	4-OBzl	H
E-112	6,8-$(OMe)_2$	H	H
E-113	6,8-$(OMe)_2$	2-OBzl	H
E-114	6,8-$(OMe)_2$	3-OBzl	H
E-115	6,8-$(OMe)_2$	4-OBzl	H

(Table 6)



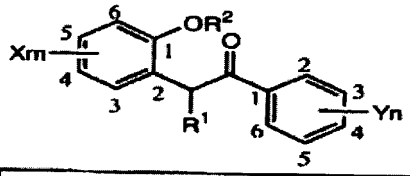
(I-F)

No.	Xm	Yn	R
F-1	4-OMe	4-Ph	H
F-2	4-OMe	2-OMe	H
F-3	4-OMe	3-OMe	H
F-4	4-OMe	4-OMe	H
F-5	4-OMe	2-OBzl	H
F-6	4-OMe	3-OBzl	H
F-7	4-OMe	4-OBzl	H
F-8	4-OMe	2,4-$(OH)_2$	H
F-9	4-OMe	2-OBzl-4-OH	H
F-10	4-OMe	2,4-$(OBzl)_2$	H
F-11	5-OMe	2,4-$(OH)_2$	H
F-12	5-OMe	2-OBzl-4-OH	H
F-13	5-OMe	2,4-$(OBzl)_2$	H
F-14	6-OMe	4-Ph	H
F-15	6-OMe	2-OMe	H
F-16	6-OMe	3-OMe	H
F-17	6-OMe	4-OMe	H
F-18	6-OMe	2-OBzl	H
F-19	6-OMe	3-OBzl	H
F-20	6-OMe	4-OBzl	H
F-21	6-OMe	2,4-$(OH)_2$	H
F-22	6-OMe	2-OBzl-4-OH	H
F-23	6-OMe	2,4-$(OBzl)_2$	H
F-24	6-OMe	2,4-$(OBzl)_2$	Me
F-25	7-OMe	2,4-$(OH)_2$	H
F-26	7-OMe	2-OBzl-4-OH	H
F-27	7-OMe	2,4-$(OBzl)_2$	H
F-28	4,5-$(OMe)_2$	2-OBzl	H
F-29	4,5-$(OMe)_2$	3-OBzl	H
F-30	4,5-$(OMe)_2$	4-OBzl	H
F-31	4,6-$(OMe)_2$	4-Ph	H
F-32	4,6-$(OMe)_2$	2-OMe	H
F-33	4,6-$(OMe)_2$	3-OMe	H
F-34	4,6-$(OMe)_2$	4-OMe	H
F-35	4,6-$(OMe)_2$	2-OBzl	H

(Table 6 continued)

F-36	4,6-$(OMe)_2$	3-OBzl	H
F-37	4,6-$(OMe)_2$	4-OBzl	H
F-38	4,6-$(OMe)_2$	2,4-$(OH)_2$	H
F-39	4,6-$(OMe)_2$	2-OBzl-4-OH	H
F-40	4,6-$(OMe)_2$	2,4-$(OBzl)_2$	H
F-41	4,6-$(OMe)_2$	2,4-$(OBzl)_2$	Me
F-42	4,7-$(OMe)_2$	2-OBzl	H
F-43	4,7-$(OMe)_2$	3-OBzl	H
F-44	4,7-$(OMe)_2$	4-OBzl	H
F-45	5,6-$(OMe)_2$	2-OBzl	H
F-46	5,6-$(OMe)_2$	3-OBzl	H
F-47	5,6-$(OMe)_2$	4-OBzl	H
F-48	6,7-$(OMe)_2$	2-OBzl	H
F-49	6,7-$(OMe)_2$	3-OBzl	H
F-50	6,7-$(OMe)_2$	4-OBzl	H
F-51	4,6-$(OMe)_2$-5-Me	2-OBzl	H
F-52	4,6-$(OMe)_2$-5-Me	3-OBzl	H
F-53	4,6-$(OMe)_2$-5-Me	4-OBzl	H
F-54	4,6-$(OMe)_2$-5-Me	4-Ph	H
F-55	4,6-$(OMe)_2$-5-prenyl	2-OBzl	H
F-56	4,6-$(OMe)_2$-5-prenyl	3-OBzl	H
F-57	4,6-$(OMe)_2$-5-prenyl	4-OBzl	H
F-58	4,6-$(OMe)_2$-5-prenyl	4-Ph	H

(Table 7)



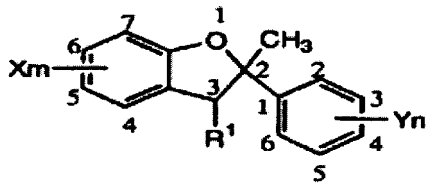
(I-G)

No.	Xm	Yn	R^1	R^2
G-1	3-OMe	2,4-$(OMe)_2$	H	COMe
G-2	3-OMe	2,4-$(OBzl)_2$	H	COMe
G-3	4-OMe	2,4-$(OBzl)_2$	H	COMe
G-4	5-OMe	2,4-$(OMe)_2$	H	COMe
G-5	5-OMe	2,4-$(OBzl)_2$	H	COMe
G-6	6-OMe	2,4-$(OBzl)_2$	H	COMe
G-7	3,4-$(OMe)_2$	4-Ph	H	COMe
G-8	3,4-$(OMe)_2$	2,4-$(OH)_2$	H	COMe
G-9	3,4-$(OMe)_2$	2,4-$(OMe)_2$	H	COMe
G-10	3,4-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe
G-11	3,5-$(OMe)_2$	2-Ph	H	COMe
G-12	3,5-$(OMe)_2$	4-Ph	H	H
G-13	3,5-$(OMe)_2$	4-Ph	H	COMe
G-14	3,5-$(OMe)_2$	4-Ph	Me	COMe
G-15	3,5-$(OMe)_2$	2-OBzl	H	COMe
G-16	3,5-$(OMe)_2$	3-OBzl	H	COMe
G-17	3,5-$(OMe)_2$	4-OBzl	H	COMe
G-18	3,5-$(OMe)_2$	2,4-Me_2	H	H
G-19	3,5-$(OMe)_2$	2,4-Me_2	H	COMe
G-20	3,5-$(OMe)_2$	2,4-Me_2	Me	COMe
G-21	3,5-$(OMe)_2$	2,4-$(OH)_2$	H	COMe
G-22	3,5-$(OMe)_2$	2,4-$(OMe)_2$	H	COMe
G-23	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	H	H
G-24	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe
G-25	3,5-$(OMe)_2$	2,4-$(OBzl)_2$	Me	COMe
G-26	3,6-$(OMe)_2$	4-Ph	H	COMe
G-27	3,6-$(OMe)_2$	2,4-$(OH)_2$	H	COMe
G-28	3,6-$(OMe)_2$	2,4-$(OMe)_2$	H	COMe
G-29	3,6-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe
G-30	4,5-$(OMe)_2$	4-Ph	H	COMe

(Table 7 continued)

G-31	4,5-$(OMe)_2$	2,4-$(OH)_2$	H	COMe
G-32	4,5-$(OMe)_2$	2,4-$(OMe)_2$	H	COMe
G-33	4,5-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe
G-34	5,6-$(OMe)_2$	4-Ph	H	COMe
G-35	5,6-$(OMe)_2$	2,4-$(OH)_2$	H	COMe
G-36	5,6-$(OMe)_2$	2,4-$(OMe)_2$	H	COMe
G-37	5,6-$(OMe)_2$	2,4-$(OBzl)_2$	H	COMe
G-38	3,5-$(OMe)_2$-4-Me	2-OMe	H	COMe
G-39	3,5-$(OMe)_2$-4-Me	3-OMe	H	COMe
G-40	3,5-$(OMe)_2$-4-Me	4-OMe	H	COMe
G-41	3,5-$(OMe)_2$-4-Me	2-OBzl	H	COMe
G-42	3,5-$(OMe)_2$-4-Me	3-OBzl	H	COMe
G-43	3,5-$(OMe)_2$-4-Me	4-OBzl	H	COMe
G-44	3,5-$(OMe)_2$-4-Me	2,4-Me_2	H	COMe
G-45	3,5-$(OMe)_2$-4-Me	2,4-$(OH)_2$	H	COMe
G-46	3,5-$(OMe)_2$-4-Me	2,4-$(OMe)_2$	H	COMe
G-47	3,5-$(OMe)_2$-4-Me	2,4-$(OBzl)_2$	H	H
G-48	3,5-$(OMe)_2$-4-Me	2,4-$(OBzl)_2$	H	COMe
G-49	3,5-$(OMe)_2$-4-prenyl	2-OMe	H	COMe
G-50	3,5-$(OMe)_2$-4-prenyl	3-OMe	H	COMe
G-51	3,5-$(OMe)_2$-4-prenyl	4-OMe	H	COMe
G-52	3,5-$(OMe)_2$-4-prenyl	2-OBzl	H	COMe
G-53	3,5-$(OMe)_2$-4-prenyl	3-OBzl	H	COMe
G-54	3,5-$(OMe)_2$-4-prenyl	4-OBzl	H	COMe
G-55	3,5-$(OMe)_2$-4-prenyl	2,4-Me_2	H	COMe
G-56	3,5-$(OMe)_2$-4-prenyl	2,4-$(OH)_2$	H	COMe
G-57	3,5-$(OMe)_2$-4-prenyl	2,4-$(OMe)_2$	H	COMe
G-58	3,5-$(OMe)_2$-4-prenyl	2,4-$(OBzl)_2$	H	H
G-59	3,5-$(OMe)_2$-4-prenyl	2,4-$(OBzl)_2$	H	COMe
G-60	3,5-$(OMe)_2$-4-prenyl	2,4-$(OBzl)_2$	Me	COMe

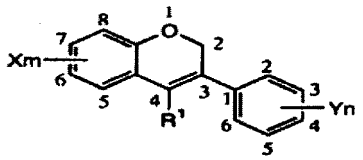
(Table 8)



(I-H)

No.	Xm	Yn	R
H-1	4-OMe	2-OBzl	H
H-2	4-OMe	2,4-$(OBzl)_2$	H
H-3	5-OMe	2-OBzl	H
H-4	5-OMe	2,4-$(OBzl)_2$	H
H-5	6-OMe	2-OBzl	H
H-6	6-OMe	2,4-$(OBzl)_2$	H
H-7	7-OMe	2-OBzl	H
H-8	7-OMe	2,4-$(OBzl)_2$	H
H-9	4,5-$(OMe)_2$	2-OBzl	H
H-10	4,5-$(OMe)_2$	2,4-$(OBzl)_2$	H
H-11	4,6-$(OMe)_2$	2-OBzl	H
H-12	4,6-$(OMe)_2$	2-OBzl	Me
H-13	4,6-$(OMe)_2$	3-OBzl	H
H-14	4,6-$(OMe)_2$	4-OBzl	H
H-15	4,6-$(OMe)_2$	2,4-$(OH)_2$	H
H-16	4,6-$(OMe)_2$	2-OH-4-OBzl	H
H-17	4,6-$(OMe)_2$	2-OBzl-4-OH	H
H-18	4,6-$(OMe)_2$	2,4-$(OBzl)_2$	H
H-19	4,6-$(OMe)_2$	2,4-$(OBzl)_2$	Me
H-20	4,7-$(OMe)_2$	2-OBzl	H
H-21	4,7-$(OMe)_2$	2,4-$(OBzl)_2$	H
H-22	5,6-$(OMe)_2$	2-OBzl	H
H-23	5,6-$(OMe)_2$	2,4-$(OBzl)_2$	H
H-24	5,7-$(OMe)_2$	2-OBzl	H
H-25	5,7-$(OMe)_2$	2,4-$(OBzl)_2$	H
H-26	4,6-$(OMe)_2$-5-Me	2,4-$(OH)_2$	H
H-27	4,6-$(OMe)_2$-5-Me	2,4-$(OBzl)_2$	H
H-28	4,6-$(OMe)_2$-5-prenyl	2,4-$(OH)_2$	H
H-29	4,6-$(OMe)_2$-5-prenyl	2,4-$(OBzl)_2$	H

(Table 9)



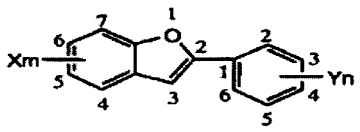
(I-J)

No.	Xm	Yn	R
J-1	H	H	H
J-2	H	3-NO_2	H
J-3	H	4-F	H
J-4	H	4-CH_3	H
J-5	H	4-CO_2H	H
J-6	6-Cl	H	H
J-7	6-Cl	3-NO_2	H
J-8	6-Cl	4-F	H
J-9	6-Cl	4-CH_3	H
J-10	5-OMe	H	H
J-11	5-OMe	2-CF_3	H
J-12	5-OMe	2-OBzl	H
J-13	5-OMe	3-OBzl	H
J-14	5-OMe	3-NO_2	H
J-15	5-OMe	4-F	H
J-16	5-OMe	4-CH_3	H
J-17	5-OMe	4-OBzl	H
J-18	5-OMe	4-CO_2H	H
J-19	6-OMe	2-OBzl	H
J-20	6-OMe	3-OBzl	H
J-21	6-OMe	4-OBzl	H
J-22	7-OMe	2-OBzl	H
J-23	7-OMe	3-OBzl	H
J-24	7-OMe	4-OBzl	H
J-25	8-OMe	H	H
J-26	8-OMe	2-CF_3	H
J-27	8-OMe	2-OBzl	H
J-28	8-OMe	3-OBzl	H
J-29	8-OMe	3-NH_2	H
J-30	8-OMe	3-NO_2	H

(Table 9 continued)

J-31	8-OMe	4-F	H
J-32	8-OMe	4-CH_3	H
J-33	8-OMe	4-OBzl	H
J-34	8-OMe	4-CO_2H	H
J-35	5,6-$(OMe)_2$	H	H
J-36	5,6-$(OMe)_2$	2-OBzl	H
J-37	5,6-$(OMe)_2$	3-OBzl	H
J-38	5,6-$(OMe)_2$	4-OBzl	H
J-39	5,7-$(OMe)_2$	H	H
J-40	5,7-$(OMe)_2$	2-OMe	H
J-41	5,7-$(OMe)_2$	2-OBzl	H
J-42	5,7-$(OMe)_2$	2-OBzl	Me
J-43	5,7-$(OMe)_2$	3-OMe	H
J-44	5,7-$(OMe)_2$	3-OBzl	H
J-45	5,7-$(OMe)_2$	3-OBzl	Me
J-46	5,7-$(OMe)_2$	4-OMe	H
J-47	5,7-$(OMe)_2$	4-OBzl	H
J-48	5,7-$(OMe)_2$	4-OBzl	Me
J-49	5,8-$(OMe)_2$	H	H
J-50	5,8-$(OMe)_2$	2-OBzl	H
J-51	5,8-$(OMe)_2$	3-OBzl	H
J-52	5,8-$(OMe)_2$	4-OBzl	H
J-53	6,7-$(OMe)_2$	H	H
J-54	6,7-$(OMe)_2$	2-OBzl	H
J-55	6,7-$(OMe)_2$	3-OBzl	H
J-56	6,7-$(OMe)_2$	4-OBzl	H
J-57	6,8-$(OMe)_2$	H	H
J-58	6,8-$(OMe)_2$	2-OBzl	H
J-59	6,8-$(OMe)_2$	3-OBzl	H
J-60	6,8-$(OMe)_2$	4-OBzl	H
J-61	7,8-$(OMe)_2$	H	H
J-62	7,8-$(OMe)_2$	2-OBzl	H
J-63	7,8-$(OMe)_2$	3-OBzl	H
J-64	7,8-$(OMe)_2$	4-OBzl	H

(Table 10)



(I-K)

No.	Xm	Yn
K-1	H	2,4-$(OTBS)_2$
K-2	4-OMe	4-OH
K-3	4-OMe	4-OBzl
K-4	4-OMe	2,4-$(OBzl)_2$
K-5	4-OMe	2,4-$(OMOM)_2$
K-6	4-OMe	2,4-$(OTBS)_2$
K-7	5-OMe	4-OH
K-8	5-OMe	4-OBzl
K-9	5-OMe	2,4-$(OBzl)_2$
K-10	5-OMe	2,4-$(OMOM)_2$
K-11	5-OMe	2,4-$(OTBS)_2$
K-12	6-OMe	4-OH
K-13	6-OMe	4-OBzl
K-14	6-OMe	2,4-$(OBzl)_2$
K-15	6-OMe	2,4-$(OMOM)_2$
K-16	6-OMe	2,4-$(OTBS)_2$
K-17	7-OMe	4-OH
K-18	7-OMe	4-OBzl
K-19	7-OMe	2,4-$(OBzl)_2$
K-20	7-OMe	2,4-$(OMOM)_2$
K-21	7-OMe	2,4-$(OTBS)_2$
K-22	4,5-$(OMe)_2$	4-OH
K-23	4,5-$(OMe)_2$	4-OBzl
K-24	4,5-$(OMe)_2$	2,4-$(OBzl)_2$
K-25	4,5-$(OMe)_2$	2,4-$(OMOM)_2$
K-26	4,5-$(OMe)_2$	2,4-$(OTBS)_2$
K-27	4,6-$(OH)_2$	2,4-$(OTBS)_2$
K-28	4-OH-6-OMe	2,4-$(OTBS)_2$
K-29	4-OMe-6-OH	2,4-$(OTBS)_2$
K-30	4,6-$(OMe)_2$	H

(Table 10 continued)

K-31	4,6-$(OMe)_2$	2-Cl
K-32	4,6-$(OMe)_2$	2-OH
K-33	4,6-$(OMe)_2$	3-OH
K-34	4,6-$(OMe)_2$	4-OH
K-35	4,6-$(OMe)_2$	2-OBu^t
K-36	4,6-$(OMe)_2$	4-OBu^t
K-37	4,6-$(OMe)_2$	2-OBzl
K-38	4,6-$(OMe)_2$	3-OBzl
K-39	4,6-$(OMe)_2$	4-OBzl
K-40	4,6-$(OMe)_2$	2-(2-ClBzlO)
K-41	4,6-$(OMe)_2$	2-(3-ClBzlO)
K-42	4,6-$(OMe)_2$	2-(4-ClBzlO)
K-43	4,6-$(OMe)_2$	2-OPh
K-44	4,6-$(OMe)_2$	2-CO_2H
K-45	4,6-$(OMe)_2$	2-CO_2Me
K-46	4,6-$(OMe)_2$	2-$CO_2{}^iPr$
K-47	4,6-$(OMe)_2$	2-CO_2Bzl
K-48	4,6-$(OMe)_2$	2-NH_2
K-49	4,6-$(OMe)_2$	2-N=CHPh
K-50	4,6-$(OMe)_2$	2-NHBzl
K-51	4,6-$(OMe)_2$	2-NO_2
K-52	4,6-$(OMe)_2$	2,4-$(OH)_2$
K-53	4,6-$(OMe)_2$	2-OH-4-OBzl
K-54	4,6-$(OMe)_2$	2-OH-4-OTBS
K-55	4,6-$(OMe)_2$	2-OBzl-4-OH
K-56	4,6-$(OMe)_2$	2,4-$(OMe)_2$
K-57	4,6-$(OMe)_2$	2,4-$(OBzl)_2$
K-58	4,6-$(OMe)_2$	2,4-$(OMOM)_2$
K-59	4,6-$(OMe)_2$	2,4-$(OTBS)_2$
K-60	4,6-$(OMe)_2$	2,4-$(OCH_2CO_2H)_2$
K-61	4,6-$(OMe)_2$	2,4-$(OCH_2CO_2Et)_2$
K-62	4,6-$(OMe)_2$	2,4-$(OCH_2CO_2Na)_2$
K-63	4,6-$(OMe)_2$	2,4-(4-picolyloxy)$_2$
K-64	4,7-$(OMe)_2$	4-OH
K-65	4,7-$(OMe)_2$	4-OBzl

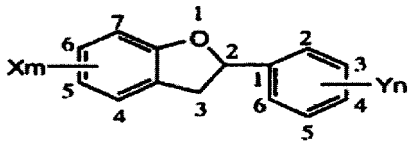
(Table 10 continued)

K-66	4,7-$(OMe)_2$	2,4-$(OBzl)_2$
K-67	4,7-$(OMe)_2$	2,4-$(OMOM)_2$
K-68	4,7-$(OMe)_2$	2,4-$(OTBS)_2$
K-69	5,6-$(OMe)_2$	4-OH
K-70	5,6-$(OMe)_2$	4-OBzl
K-71	5,6-$(OMe)_2$	2,4-$(OBzl)_2$
K-72	5,6-$(OMe)_2$	2,4-$(OMOM)_2$
K-73	5,6-$(OMe)_2$	2,4-$(OTBS)_2$
K-74	5,7-$(OMe)_2$	4-OH
K-75	5,7-$(OMe)_2$	4-OBzl
K-76	5,7-$(OMe)_2$	2,4-$(OBzl)_2$
K-77	5,7-$(OMe)_2$	2,4-$(OMOM)_2$
K-78	5,7-$(OMe)_2$	2,4-$(OTBS)_2$
K-79	6,7-$(OMe)_2$	4-OH
K-80	6,7-$(OMe)_2$	4-OBzl
K-81	6,7-$(OMe)_2$	2,4-$(OBzl)_2$
K-82	6,7-$(OMe)_2$	2,4-$(OMOM)_2$
K-83	6,7-$(OMe)_2$	2,4-$(OTBS)_2$
K-84	4,6-$(OMe)_2$-5-Me	4-OH
K-85	4,6-$(OMe)_2$-5-Me	4-OBzl
K-86	4,6-$(OMe)_2$-5-Me	2,4-$(OBzl)_2$
K-87	4,6-$(OMe)_2$-5-Me	2,4-$(OMOM)_2$

(Table 10 continued)

K-88	4,6-$(OMe)_2$-5-Me	2,4-$(OTBS)_2$
K-89	4,6-$(OMe)_2$-5-prenyl	2-prenyloxy-4-OH
K-90	4,6-$(OMe)_2$-5-prenyl	2-OH-4-OTBS
K-91	4,6-$(OMe)_2$-5-prenyl	2,4-$(prenyloxy)_2$
K-92	4,6-$(OMe)_2$-5-prenyl	2,4-$(OTBS)_2$
K-93	4,6-$(OMe)_2$-5-prenyl	2,4-$(OH)_2$

(Table 11)



(I-L)

No.	Xm	Yn
L-1	H	2,4-$(OTBS)_2$
L-2	4-OMe	4-OH
L-3	4-OMe	4-OBzl
L-4	4-OMe	2,4-$(OBzl)_2$
L-5	4-OMe	2,4-$(OMOM)_2$
L-6	4-OMe	2,4-$(OTBS)_2$
L-7	5-OMe	4-OH
L-8	5-OMe	4-OBzl
L-9	5-OMe	2,4-$(OBzl)_2$
L-10	5-OMe	2,4-$(OMOM)_2$
L-11	5-OMe	2,4-$(OTBS)_2$
L-12	6-OMe	4-OH
L-13	6-OMe	4-OBzl
L-14	6-OMe	2,4-$(OBzl)_2$
L-15	6-OMe	2,4-$(OMOM)_2$
L-16	6-OMe	2,4-$(OTBS)_2$
L-17	7-OMe	4-OH
L-18	7-OMe	4-OBzl
L-19	7-OMe	2,4-$(OBzl)_2$
L-20	7-OMe	2,4-$(OMOM)_2$
L-21	7-OMe	2,4-$(OTBS)_2$
L-22	4,5-$(OMe)_2$	4-OH
L-23	4,5-$(OMe)_2$	4-OBzl
L-24	4,5-$(OMe)_2$	2,4-$(OBzl)_2$
L-25	4,5-$(OMe)_2$	2,4-$(OMOM)_2$
L-26	4,5-$(OMe)_2$	2,4-$(OTBS)_2$
L-27	4,6-$(OH)_2$	2,4-$(OTBS)_2$
L-28	4-OH-6-OMe	2,4-$(OTBS)_2$
L-29	4-OMe-6-OH	2,4-$(OTBS)_2$
L-30	4,6-$(OMe)_2$	H

(Table 11 continued)

L-31	4,6-$(OMe)_2$	2-Cl
L-32	4,6-$(OMe)_2$	2-OH
L-33	4,6-$(OMe)_2$	3-OH
L-34	4,6-$(OMe)_2$	4-OH
L-35	4,6-$(OMe)_2$	2-OBu^t
L-36	4,6-$(OMe)_2$	4-OBu^t
L-37	4,6-$(OMe)_2$	2-OBzl
L-38	4,6-$(OMe)_2$	3-OBzl
L-39	4,6-$(OMe)_2$	4-OBzl
L-40	4,6-$(OMe)_2$	2-(2-ClBzlO)
L-41	4,6-$(OMe)_2$	2-(3-ClBzlO)
L-42	4,6-$(OMe)_2$	2-(4-ClBzlO)
L-43	4,6-$(OMe)_2$	2-OPh
L-44	4,6-$(OMe)_2$	2-CO_2H
L-45	4,6-$(OMe)_2$	2-CO_2Me
L-46	4,6-$(OMe)_2$	2-$CO_2{}^iPr$
L-47	4,6-$(OMe)_2$	2-CO_2Bzl
L-48	4,6-$(OMe)_2$	2-NH_2
L-49	4,6-$(OMe)_2$	2-N=CHPh
L-50	4,6-$(OMe)_2$	2-NHBzl
L-51	4,6-$(OMe)_2$	2-NO_2
L-52	4,6-$(OMe)_2$	2,4-$(OH)_2$
L-53	4,6-$(OMe)_2$	2-OH-4-OBzl
L-54	4,6-$(OMe)_2$	2-OH-4-OTBS
L-55	4,6-$(OMe)_2$	2-OBzl-4-OH
L-56	4,6-$(OMe)_2$	2,4-$(OMe)_2$
L-57	4,6-$(OMe)_2$	2,4-$(OBzl)_2$
L-58	4,6-$(OMe)_2$	2,4-$(OMOM)_2$
L-59	4,6-$(OMe)_2$	2,4-$(OTBS)_2$
L-60	4,6-$(OMe)_2$	2,4-$(OCH_2CO_2H)_2$
L-61	4,6-$(OMe)_2$	2,4-$(OCH_2CO_2Et)_2$
L-62	4,6-$(OMe)_2$	2,4-$(OCH_2CO_2Na)_2$
L-63	4,6-$(OMe)_2$	2,4-(4-picolyloxy)$_2$
L-64	4,7-$(OMe)_2$	4-OH
L-65	4,7-$(OMe)_2$	4-OBzl

(Table 11 continued)

L-66	4,7-$(OMe)_2$	2,4-$(OBzl)_2$
L-67	4,7-$(OMe)_2$	2,4-$(OMOM)_2$
L-68	4,7-$(OMe)_2$	2,4-$(OTBS)_2$
L-69	5,6-$(OMe)_2$	4-OH
L-70	5,6-$(OMe)_2$	4-OBzl
L-71	5,6-$(OMe)_2$	2,4-$(OBzl)_2$
L-72	5,6-$(OMe)_2$	2,4-$(OMOM)_2$
L-73	5,6-$(OMe)_2$	2,4-$(OTBS)_2$
L-74	5,7-$(OMe)_2$	4-OH
L-75	5,7-$(OMe)_2$	4-OBzl
L-76	5,7-$(OMe)_2$	2,4-$(OBzl)_2$
L-77	5,7-$(OMe)_2$	2,4-$(OMOM)_2$
L-78	5,7-$(OMe)_2$	2,4-$(OTBS)_2$
L-79	6,7-$(OMe)_2$	4-OH
L-80	6,7-$(OMe)_2$	4-OBzl
L-81	6,7-$(OMe)_2$	2,4-$(OBzl)_2$
L-82	6,7-$(OMe)_2$	2,4-$(OMOM)_2$
L-83	6,7-$(OMe)_2$	2,4-$(OTBS)_2$
L-84	4,6-$(OMe)_2$-5-Me	4-OH
L-85	4,6-$(OMe)_2$-5-Me	4-OBzl
L-86	4,6-$(OMe)_2$-5-Me	2,4-$(OBzl)_2$
L-87	4,6-$(OMe)_2$-5-Me	2,4-$(OMOM)_2$
L-88	4,6-$(OMe)_2$-5-Me	2,4-$(OTBS)_2$
L-89	4,6-$(OMe)_2$-5-prenyl	2-prenyloxy-4-OH
L-90	4,6-$(OMe)_2$-5-prenyl	2-OH-4-OTBS
L-91	4,6-$(OMe)_2$-5-prenyl	2,4-$(prenyloxy)_2$
L-92	4,6-$(OMe)_2$-5-prenyl	2,4-$(OTBS)_2$

Prodrugs are derivatives of compounds pursuant to the present invention with groups capable of chemical or metabolic decomposition. They are compounds that become the compounds pursuant to the present invention with pharmaceutical activity in vivo under physiological conditions or as a result of solvolysis. Methods of selecting suitable prodrug derivatives of their production are stated in Design of prodrugs, Elsevier, Amsterdam 1985, for example. Prodrugs such as ester derivatives produced by reacting originally acidic compounds with suitable alcohols or amido derivatives produced by reacting originally acidic compounds with suitable amines are examples when the compound pursuant to the present invention has carboxyls. Especially desirable esters as prodrugs include methyl esters, ethyl esters, n-propyl esters, isopropyl esters, n-butyl esters, isobutyl esters, tert-butyl esters, morpholino ethyl esters, and N,N-diethyl glycol amide esters. Examples of prodrugs when the compound pursuant to the present invention has hydroxys are acyloxy derivatives produced by reacting compounds having hydroxys with suitable acyl halides or suitable anhydrides. Especially desirable examples of acyloxys as prodrugs include $-OCOC_2H_2$, -OCO (tert-Bu), $-OCOC_{15}H_{31}$, -OCO (m-COONa-Ph), $-OCOCH_2CH_2COONa$, $-OCOCH(NH_2)CH_3$, $-OCOCH_2N(CH_3)_2$. Examples of prodrugs when the compound pursuant to the present invention has aminos are amide derivatives produced by reacting compounds having aminos with suitable acid halides or suitable mixed acid anhydrides. Especially desirable examples of amides as prodrugs include $-NHCO(CH_2)_{20}CH_3$, $-NHCOCH(NH_2)CH_2$, etc.

"Salts" of target compounds pursuant to the present invention preferably would be pharmacologically permissible salts, examples being salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino salts. Salts with inorganic bases include alkali metal salts such as sodium salts or potassium salts; salts with alkaline earth metals such as calcium salts, magnesium salts, barium salts, as well as aluminum salts and ammonium salts. Examples of organic bases include salts with trimethyl amines, triethyl amines, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexyl amine, N,N=-dibenzylethylene diamine, etc. Salts with inorganic acids include salts with hydrochloric acid, hydrofluoric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, perchloric acid, hydriodic acid, etc. Salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, mandelic acid, ascorbic acid, lactic acid, gluconic acid, methane sulfonic acid, p-toluene sulfonic acid, and benzene sulfonic acid. Salts with basic amino acids include salts with arginine, lysine, and ornithine. Salts with acidic amino acids include salts with aspartic acid or glutamic acid.

The term "solvate" in the specification connotes solvates or hydrates with organic solvents, for example. Solvates in pharmacologically permissible solvents are preferable. Hydrates are more preferable.

Pharmacologically permissible hydrates are preferable as "hydrates" of the target compound pursuant to the present invention , and includes hydrate salts. Concrete examples include monohydrates, dihydrates, and hexahydrates.

"Immunopotentiating effects" connotes potentiation of the immune function, specifically, elevation of defense function of the body in the event of viral or bacterial (including secondary) infections (for example, opportunistic infections, refractory infections), potentiation of the immune function in patients with malignant tumors who have suffered attenuation of the immune function to thereby permit aggressive immunological treatment of cancer cells, as well as activation of bio-defense reactions in patients with immune function failure as in the case of radiation-induced disorders. It is also effective in cases of attenuated immunity due to administration of antitumor agents. The compound pursuant to the present invention can be used preferably as an immunopotentiating agent (excluding antitumor agents).

"Immunopotentiating activity" connotes activity associated with aforementioned immunopotentiating effects.

The quantitative method of measuring immunopotentiating effects is to measure the blastogenic rate or cell metabolic activity.

The blastogenic rate is measured by measuring the effects on the blastogenic reaction of mouse splenic cells. Concretely, the following measurement method is possible:

Trial samples are formed by diluting analyte dissolved in dimethyl sulfoxide (DMSO) solution in two-fold stages in a 96-well microplate using 10% FBS (1 well/100 μl).

Spleens of BALB/c mice were aseptically isolated, gently washed over a wire mesh while sterile physiological saline solution was added slowly, and the filtrate was passed through a nylon mesh (product of Becton Dickinson: pore size 70 μm) to complete preparation of a single-cell suspension.

The splenic cells were washed twice with sterile physiological saline solution followed by suspension in 10%-FCS added RPM 11640 containing 1 μg/ml of concanavalin A (abbreviated ConA: product of Sigma-Aldrich Corporation, U.S.) and antibiotics (product of Sigma-Aldrich Corporation, antibiotic, antimycotic). The diluted trial samples were dispensed in 100 μl portions in a 96-well microplate so as to reach 3 x 105 cell/100 μl/well.

That was followed by incubation for 3 hours at 37^0C in 5% carbon dioxide and measurement of the blastogenic reaction of lymphocytes by the MTT reduction method [Mosmann T., Journal of Immunological Method, Vol. 65, p. 55, 1983]. The blastogenic rate is quantified as the proportion when the blastogenic reaction in a specimen-free section is taken as one. Immunopotentiating effects are judged to be present when the blastogenic rate exceeds 1.

Cell metabolic activity represents measurement of the mitochondria metabolic activity of myeloid cells by the MIT reduction method following the addition of trial compound at a concentration of 0.39 to 12.5 μg/ml to RPM11640 culture medium containing 2 x 10^6 cell/ml of BALB/C mouse myeloid cells, antibiotics, and 10% fetal calf serum, and incubation for 5 days at

37^0C in 5% carbon dioxide. Immunopotentiating effects are judged to be present when the metabolic degree, taking the cell metabolic degree in a specimen-free section as 1, exceeds 1.

"Myeloid cell metabolic stimulation effects" broadly includes the following leukocyte growth effects and lymphocyte function regulatory effects. It connotes the effects of stimulating myeloid cell growth via various mechanisms of effect.

Lymphocytes are cells that recognize external antigens via surface receptors. They change into cells that play the most important roles in immunity phenomena through cell division and maturation. Antigens and lectins are some of the substances that trigger lymphocyte activation. Biochemical changes are induced in cell membranes and cytoplasm through activation of these, but "lymphocyte function regulation effects" in the specification connotes the effect of regulating the immunity phenomena wherein lymphocytes are the main participants.

Leukocytes are one constituent of hemocytes that comprise neutrocytes, eosinocytes, basocytes, monocytes, and lymphocytes (T lymphocytes, B lymphocytes). Leukocytes other than T lymphocyte grow-differentiate-mature in bone marrow, and T lymphocytes grow in bone marrow but grow-differentiate-mature subsequently in the thymus gland. Due to leukocyte growth effects, they can be used as therapeutic agents or prophylactics for leukocytopenia that develops from various causes, including radiotherapy and chemotherapy for cancer. They can also be utilized as agents that promptly restore the white cell count or as hematopoietic promoters during bone marrow transplants.

Synergy with substances among compounds of the application that have other immunopotentiating effects, such as the growth effects of G-CSF, is anticipated. These can be used in the treatment of autoimmune diseases such as hypoplastic anemia or idiopathic thrombocytopenic purpura accompanying thrombocytopenia following bone marrow transplant or blood platelet decrease.

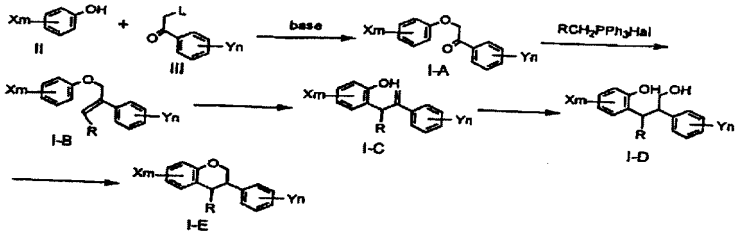
Examples of compositions comprise medical compositions (including topical medicine), veterinary medicine (livestock medicine, fisheries medicine), as well as food compositions and cosmetic compositions. Accordingly, the product of the present invention can be used in various applications. Specifically, topical medicinal agents, cosmetics, foods, foods with specific health effects, feed or livestock feed are blended with compounds pursuant to the present invention as immunopotentiating agents in humans or animals or in the expectation of an immune function effect.

(Method of Producing Compounds Pursuant to the Present Invention)

Compounds used in the present invention, salts thereof, prodrugs or hydrates thereof can be easily produced by known methods. Concrete examples of said methods are cited below.

Methods of synthesizing compounds of formula (I-A), (I-B), (I-C), (I-D), and (I-E) are exemplified in the following schemes.

(Reaction scheme 1)



Compound of formula (I-A)
The compound of formula (I-A) is obtained by reacting the compound of formula II with the compound of formula III in the presence of a base. In a concrete example, the compound is obtained by the same method as the method cited in Working Example 1.

Any base that can promote the reaction may be used without any specific limitation. Inorganic bases or organic bases would be preferable.

The reaction temperature should be a temperature at which the reaction can adequately proceed, but there is no limitation on the temperature. The temperature preferably would be in the range of 0^0C to 100^0C.

The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.5 to 48 hours, more preferably 1 hour to 24 hours.

The amount of compound of formula II that is used should be in the range of 0.5 to 4 equivalents to the compound of formula III, more preferably 0.9 to 1.5 equivalents.

(Compound of formula (I-B))

The compound of formula (I-B) would be derived by acting the compound RCH_2PPh_3Hal on the compound of formula (I-A). Concretely, it is the same method as the method cited in Working Example 2.

Any base that can promote the reaction may be used without any specific limitation. Inorganic bases or organic bases would be preferable.

The reaction temperature should be a temperature at which the reaction can adequately proceed, but there is no limitation on the temperature. The temperature preferably would be in the range of -20^0C to 50^0C.

The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.5 to 48 hours, more preferably 1 hour to 24 hours.

The amount of RCH_2PPH_3Hal that is used should be in the range of 0.5 to 4 equivalents to the compound of formula (I-A), more preferably 0.9 to 1.5 equivalents.

(Compound of formula (I-C))

The compound of formula (I-C) would be derived by transposing the compound of formula (I-B). Concretely, it is the same method as the method cited in Working Example 3.

Aforementioned transposition reaction can be carried out by heating or by adding reagents, but when reagents are used, those that are commonly used in transposition reactions that had been suitably selected as a function of the type of raw-material compound may be used without specific limitation. For example, acids or bases may be used. Examples of acids include Bronsted acids typified by inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, perchloric acid, phosphoric acid) or organic acids (for example, acetic acid, formic acid, oxalic acid, methanesulfonic acid, paratoluene sulfonic acid, trifluoroacetic acid, trifluoromethanesulfonic acid), as well as such Lewis acids as boron trichloride, boron trifluoride, boron tribromide. Examples of bases include alkali metal carbonates (for example, sodium carbonate, potassium carbonate), alkali metal hydrogencarbonates (for example, sodium hydrogencarbonate, potassium hydrogencarbonate, lithium hydrogencarbonate), alkali metal hydrides (for example, sodium hydride, lithium hydride, potassium hydride), alkali metal salts hydroxides (for example, sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide), alkali metal salts iodides (for example, sodium iodide, potassium iodide), alkali metal salts alkoxides (for example, sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide, lithium methoxide), lithium diisopyl amide, tetra-n-butyl ammonium, sodium acetate anhydrous, mercury acetate.

There is no limitation on the solvent used so long as it does not adversely affect the reaction and so long as the starting substances are dissolved without obstructing the reaction. Desirable examples include alcohol solvents (for example, methanol, ethanol, n-propanol, isopropanol), ether solvents (for example, tetrahydrofuran, diethyl ether, dioxane, diisopropyl ether, dimethoxy ethane, diethylene glycol dimethyl ether), halogenated hydrocarbons (for example, tetrachloro methane, dichloro methane, dichlorobenzene, chlorobenzene, dichloro ethane, methylene chloride), aromatic hydrocarbons (for example, benzene, toluene, xylene), saturated hydrocarbons (for example, heptane, hexane), nitriles (for example, acetonitrile, isobutyrl nitrile), amides (for example, formamide, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl-2-pyrrolidone, N-methyl pyrrolidinone, hexamethylene phosphorotriamide), sulfoxides (for example, dimethyl sulfoxide, sulfolane), as well as pyridine, acetone or mixed solvents of these. The solvent would be suitably selected considering the compound solubility and reaction type.

The reaction temperature should be in the range of -78^0C to 350^0C, preferably -20^0C to 300^0C.

The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.03 to 48 hours, more preferably 0.5 hour to 10 hours.

The reaction may be carried out in the presence of argon or nitrogen.

The resulting compound may be purified by usual techniques (for example, column chromatography, recrystallization, etc.)

(Compound of formula (I-D))

The compound of formula (I-D) would be derived by adding water to the compound of formula (I-C). Concretely, it is the same method as the method cited in Working Example 4.

The compound of formula (I-D) could be produced by oxidizing the compound of formula (I-C) with oxidizing agent in a suitable solvent optionally using hydroboronation agent.

When hydroboronation agents are used, examples of hydroboronation agents would be boron, diboron, 9-borabicyclo [3.3.1] nonane (9-BBN), borohydrides (for example, sodium borohydride), and Lewis acids. They would be suitably selected as a function of the type of compound (VI). Oxidizing agents that are used would be those that are commonly used without limitation, examples being hydrogen peroxide, and peroxides (for example, tert-butyl peroxide).

There is no limitation on the solvent used so long as it does not adversely affect the reaction and so long as the starting substances do not obstruct the reaction when hydroboronation agents are employed, and desirable examples include ether solvents (for example, tetrahydrofuran, diethyl ether, dioxane, diisopropyl ether, dimethoxy ethane, diethylene glycol dimethyl ether), halogenated hydrocarbons (for example, tetrachloro methane, dichloro methane, dichlorobenzene, chlorobenzene, dichloro ethane, methylene chloride), aromatic hydrocarbons (for example, benzene, toluene, xylene), saturated hydrocarbons (for example, heptane, hexane), alcohols (for example, methanol, ethanol, n-propanol, isopropanol), water or mixed solvents of these. The solvent would be suitably selected considering the compound solubility and reaction type.

The reaction temperature should be in the range of -78^{0}C to 70^{0}C, preferably -10^{0}C to 35^{0}C.

The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.03 to 48 hours, more preferably 1 hour to 6 hours.

The oxidizing agent used in addition to aforementioned peroxides include osmium compounds (for example, potassium osmiate-dihydrate, osmium tetroxide), ruthenium oxides (for example, ruthenium oxide (IV)), selenium compounds (for example, selenium dioxide), manganese oxides

(for example, manganese peroxide, manganese dioxide), ferricyano compounds (for example, potassium ferricyanide, nitrite esters (for example, ethyl nitrite), hypochlorite compounds (for example, ethyl hypochlorite), and persulfate compounds (for example, potassium persulfate). These oxidizing agents preferably would be used in the presence of acids or bases, with the preferable acids being Lewis acids (for example, aluminum chloride) and the preferable bases being alkali metal hydroxides (for example, sodium hydroxide) or organic bases (for example, tetramethyl ethylene diamine).

There is no limitation on the solvent used when using oxidizing agents so long as it does not adversely affect the reaction and so long as the starting substances are dissolved without obstructing the reaction. Desirable examples include ether solvents (for example, tetrahydrofuran, diethyl ether, dioxane, diisopropyl ether, dimethoxy ethane, diethylene glycol dimethyl ether), halogenated hydrocarbons (for example, tetrachloro methane, dichloro methane, dichlorobenzene, chlorobenzene, dichloro ethane, methylene chloride), aromatic hydrocarbons (for example, benzene, toluene, xylene), saturated hydrocarbons (for example, heptane, hexane), nitriles (for example, acetonitrile, isobutyrl nitrile), amides (for example, formamide, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl-2-pyrrolidone, N-methyl pyrrolidinone, hexamethylene phosphorotriamide), sulfoxides (for example, dimethyl sulfoxide, sulfolane), alcohols (for example, methanol, ethanol, n-propanol, isopropanol, tert-butanol), esters (for example, ethyl acetate, butyl acetate, diethyl carbonate), water, pyridine, acetone or mixed solvents of these. The solvent would be suitably selected considering the compound solubility and reaction type.

The reaction temperature should be in the range of -78^{0}C to 70^{0}C, preferably -10^{0}C to 35^{0}C.

The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.03 to 48 hours, more preferably 1 hour to 6 hours.

The step using aforementioned hydroboronation agents and the step using oxidizing agents may be implemented in stages in the production of compounds of formula (I-C) to compounds of formula (I-D). Compounds of formula (I-D) can be produced under these reaction conditions even when employing only the step using oxidizing agents.

The resulting compounds may be purified by usual techniques (for example, column chromatography, recrystallization, etc.)

(Compounds of formula (I-E))

The compound of formula (I-E) is obtained by dehydrocyclization of the compound of formula (I-D). Concretely, it is obtained by the same method as the method cited in Working Example 5. In addition, it may be derived by hydrogenating the compound of formula (I-J), as stated in Working Example 9.

The compound of formula (I-E) can be produced by ring closure through a dehydration reaction from the compound of formula (I-D) in the presence or absence of acid or base and in the presence or absence of solvent.

There is no limitation on the acids used so long as they are commonly used in reactions. Examples of acids include Bronsted acids typified by inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, perchloric acid, phosphoric acid) or organic acids (for example, acetic acid, formic acid, oxalic acid, methanesulfonic acid, paratoluenesulfonic acid, trifluoroacetic acid, trifluoromethanesulfonic acid), Lewis acids such as boron trichloride, boron trifluoride, or boron tribromide, and combinations of phosphine, dialkylazodicarboxylate or tetraalkyl azodicarboxamide (for example, 1:1 triphenylphosphine diethylazodicarboxylate (TPP-DEAD)). There is no limitation on the bases used so long as they are commonly used in reactions. Examples include alkali metal carbonates (for example, sodium carbonate) or organic bases (for example, pyridine).

There is no limitation on the solvent used so long as it does not adversely affect the reaction and so long as the starting substances are dissolved without obstructing the reaction. Desirable examples include ether solvents (for example, tetrahydrofuran, diethyl ether, dioxane, diisopropyl ether, dimethoxy ethane, diethylene glycol dimethyl ether), halogenated hydrocarbons (for example, tetrachloro methane, dichloro methane, dichloro benzene, chloro benzene, dichloro ethane, methylene chloride), aromatic hydrocarbons (for example, benzene, toluene, xylene), saturated hydrocarbons (for example, heptane, hexane), nitriles (for example, acetonitrile, isobutyrl nitrile), amides (for example, formamide, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl-2-pyrrolidone, N-methyl pyrrolidinone, hexamethylene phosphorotriamide), sulfoxides (for example, dimethyl sulfoxide, sulfolane), as well as pyridine, acetone or mixed solvents of these. The solvent would be suitably selected considering the compound solubility and reaction type.

The reaction temperature should be in the range of -78^0C to 250^0C, preferably 0^0C to 100^0C.

The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.03 to 48 hours, more preferably 1 hour to 25 hours.

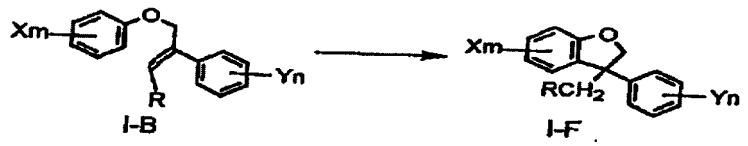
The amount of acid used should be 0.8 to 2.0 equivalents to the compound of formula (I-D).

The reaction may be carried out in the presence of argon or nitrogen.

The resulting compounds may be purified by usual techniques (for example, column chromatography, recrystallization, etc.) as required.

The method of synthesizing compounds of formula (I-F) is exemplified below in the following scheme.

(Reaction scheme 2)



(Compound of formula (I-F))

The compound of formula (I-F) is derived by acid treatment of the compound of formula (I-B).

Any acid that can promote the reaction may be used without any specific limitation. Inorganic acids or organic acids would be preferable.

The reaction temperature should be a temperature at which the reaction can adequately proceed, but there is no limitation on the temperature. The temperature preferably would be in the range of 0^0C to 100^0C.

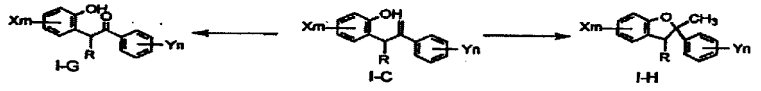
The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.5 to 48 hours, more preferably 1 hour to 24 hours.

The amount of acid that is used should be in the range of 0.1 to 20 equivalents to the compound of formula (I-B), more preferably 0.5 to 5 equivalents.

The resulting compound may be purified by usual techniques (for example, column chromatography, recrystallization, etc.) as required.

The method of synthesizing compounds of formulas (I-G) and (I-H) is exemplified below in the following scheme.

(Reaction scheme 3)



(Compound of formula (I-G))

The compound of formula (I-G) may be derived by acting CH_3PPh_3Hal on the compound of formula (I-C), for example. In a concrete example, the compound is obtained by the same method as the method cited in Working Example 2.

Any base that can promote the reaction may be used without any specific limitation. Inorganic bases or organic bases would be preferable.

The reaction temperature should be a temperature at which the reaction can adequately proceed, but there is no limitation on the temperature. The temperature preferably would be in the range of -20°C to 50°C.

The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.5 to 48 hours, more preferably 1 hour to 24 hours.

The amount of CH_3PPh_3Hal that is used should be in the range of 0.5 to 10 equivalents to the compound of formula (I-C), more preferably 0.9 to 2 equivalents.

The resulting compounds may be purified by usual techniques (for example, column chromatography, recrystallization, etc.) as required.

(Compound of formula (I-H))

The compound of formula (I-H) may be derived by acid treatment of the compound of formula (I-C). Any acid that can promote the reaction may be used without any specific limitation. Inorganic acids or organic acids would be preferable.

The reaction temperature should be a temperature at which the reaction can adequately proceed, but there is no limitation on the temperature. The temperature preferably would be in the range of 0°C to 100°C.

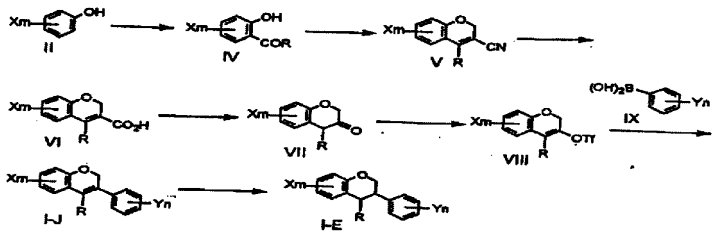
The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.5 to 48 hours, more preferably 1 hour to 24 hours.

The amount of acid that is used should be in the range of 0.1 to 20 equivalents to the compound of formula (I-C), more preferably 0.5 to 5 equivalents.

The resulting compound may be purified by usual techniques (for example, column chromatography, recrystallization, etc.) as required.

The method of synthesizing compounds of formula (I-J) is exemplified below in the following scheme.

(Reaction scheme 4)



(Compound of formula (I-J))

The compound of formula (I-J) may be derived by acting the compound of formula IX on the compound of formula VIII, for example. In a concrete example, the compound is obtained by the same method as the method cited in Working Example 2.

Any base that can promote the reaction may be used without any specific limitation. Inorganic bases or organic bases would be preferable.

The reaction temperature should be a temperature at which the reaction can adequately proceed, but there is no limitation on the temperature. The temperature preferably would be in the range of 0^0C to 150^0C.

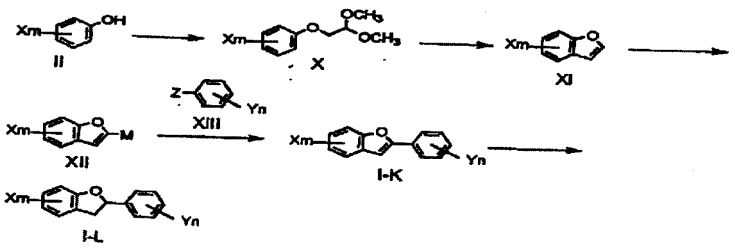
The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.5 to 48 hours, more preferably 1 hour to 24 hours.

The amount of compound of formula IX that is used should be in the range of 0.5 to 10 equivalents to the compound of formula VIII, more preferably 0.9 to 2 equivalents.

The resulting compounds may be purified by usual techniques (for example, column chromatography, recrystallization, etc.) as required.

The method of synthesizing compounds of formulas (I-K) and (I-L) is exemplified below in the following scheme.

(Reaction scheme 5)



(Compound of formula (I-K))

The compound of formula (I-K) may be derived by acting the compound of formula XIII on the compound of formula XII, for example. In a concrete example, the compound is obtained by the same method as the method cited in Working Example 10.

Any base that can promote the reaction may be used without any specific limitation. Inorganic bases or organic bases would be preferable.

The reaction temperature should be a temperature at which the reaction can adequately proceed, but there is no limitation on the temperature. The temperature preferably would be in the range of 0^0C to 150^0C.

The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.5 to 48 hours, more preferably 1 hour to 24 hours.

The amount of compound of formula XIII that is used should be in the range of 0.1 to 10 equivalents to the compound of formula XII, more preferably 0.9 to 2 equivalents.

The resulting compounds may be purified by usual techniques (for example, column chromatography, recrystallization, etc.) as required.

(Compound of formula (I-L))

The compound of formula (I-L) is obtained by hydrogenating the compound of formula (I-K). In a concrete example, the compound is obtained by the same method as the method cited in Working Example 9.

Any catalyst that can promote the reaction may be used without any specific limitation. Palladium carbonate or platinum dioxide would be preferable.

The reaction temperature should be a temperature at which the reaction can adequately proceed, but there is no limitation on the temperature. The temperature preferably would be in the range of 0^0C to 100^0C.

The reaction time varies with the solvent used, the reaction temperature, the types of raw-material compounds or the types of reaction reagents, but it preferably would be 0.5 to 48 hours, more preferably 1 hour to 24 hours.

The amount of catalyst that is used should be in the range of 0.01 to 1 equivalent to the compound of formula (I-K), more preferably 0.02 to 0.5 equivalent.

The resulting compound may be purified by usual techniques (for example, column chromatography, recrystallization, etc.) as required.

(Protecting groups)

The aminos, carboxyls, hydroxyls, carbonyls, etc., used in aforementioned series of synthesizing reactions (including the cases in which substituents are used) may be used as indicated below as protecting groups.

Examples of amino protecting groups include the type of protecting groups that form amides (for example, formyls, acetyls, chloroacetyls, dichloroacetyls, trichloroacetyls, trifluoroacetyls, acetacetyls, o-nitrophenylacetyls), the type of protecting group that form carbamates (for example, tert-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, benzhydryloxycarbonyl, 2-trimethylsilylethoxycarbonyl, 1-methyl-1-(4-biphenylyl) ethoxycarbonyl, 9-acetolylmethoxycarbonyl, 9-fluororenylmethoxycarbonyl, isonicotinyloxycarbonyl, 1-adamatyloxycarbonyl), as well as trityl and phthaloyl.

Examples of hydroxyl protecting groups include the type of protecting groups that form ethers (for example, methoxymethyl, tert-butoxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl) ethoxymethyl, benzyloxymethyl, methylthiomethyl, 2-tetrahydropyranyl, 4-methoxy-4-tetrahydropyranyl, 2-tetrahydropyranyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, o-nitrobenzyl, 2,6-dichlorobenzyl, trityl), the type of protecting groups that form silylethers (for example, trimethylsilyl, triethylsilyl, triisopropylsilyl, isopropyldimethylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, triphenylsilyl, methyldiphenylsilyl, tribenzylsilyl), and the type of protecting groups that form esters (for example, formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, pivaloyl, benzoyl, benzyloxycarbonyl, 2-bromobenzyloxycarbonyl).

Desirable examples of carboxy protecting group include the type of protecting group that form esters (for example, methyl, ethyl, tert-butyl, methoxymethyl, methoxyethoxymethyl, 2,2,2-trichloroethyl, benzyloxymethyl, 2-trimethylsilylethyl, allyl, benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl, trityl, cyclohexyl, cyclopentyl, phenacyl), and the type of

protecting group that form silyl esters (for example, trimethyl silyl, triethyl silyl, tert-butyldimethyl silyl, dimethylphenyl silyl, isopropyl dimethyl silyl).

Examples of carbonyl protecting group include the type of protecting group that forms acetals, dithioacetals, or dithioketals (for example, dimethyl, diethyl, diacetyl, dibenzyl), the type that forms optionally substituted 1,3-dioxanes or 1,3-dioxolans, the type that forms 1,3-dithiane or 1,3-dithiolane as well as the type that forms substituted hydrazone (for example, N,N-dimethyl, 2,4-dinitrophenyl).

Methods of raw materials aforementioned amino protecting groups, carbonyl protecting groups, and carboxy protecting groups include the method based on bases, the method based on acids, the method based on reduction, the method based on ultraviolet irradiation, the method based on hydrazine, the method based on phenyl hydrazine, the method based on N-methyl dithio sodium carbamate, the method based on tetrabutyl ammonium fluoride, the method based on palladium acetate, the method based on mercurous chloride, and the method based on Lewis acids. These common methods or other known techniques may be suitably selected and used.

The method based on bases is one common method of hydrolysis of amides and esters similarly to the method based on acids, and is applicable to elimination of corresponding protecting groups. Organic bases are effectively used in deprotection of amino groups protected by 9-fluorenyl methoxycarbonyl, for example. Desirable examples of bases that are used include such inorganic bases as alkali metal hydroxides (for example, lithium hydroxide, sodium hydroxide, potassium hydroxide), alkaline earth metal hydroxides (for example, magnesium hydroxide, calcium hydroxide), alkali metal carbonates (for example, sodium carbonate, potassium carbonate), alkaline earth metal carbonates (for example, magnesium carbonate, calcium carbonate), alkali metal hydrogencarbonates (for example, sodium hydrogencarbonate, potassium hydrogencarbonate), alkali metal acetates (for example, sodium acetate, potassium acetate), alkaline earth metal phosphates (for example, calcium phosphate, magnesium phosphate), alkali metal hydrogenphosphates (for example, disodium hydrogenphosphate, dipotassium hydrogenphosphate), and ammonia water, as well as organic bases such as trimethyl amine, triethyl amine, diisopropylethyl amine, pyridine, picoline, N-methylpyrrolidine, piperidine, N-methylpiperidine, N-methylmorpholine, 1,5-diazabicyclo [4.3.0] non-5-en, 1,4-diazabicyclo [2.2.2] octane, 1,8-diazabicyclo [5.4.0]-7-undecene.

The method based on acids is one common method of hydrolysis of amides, esters, silyl esters and silyl ethers, and is applicable to elimination of corresponding protecting groups. This is applicable to deprotection of protected aminos (for example, aminos protected by tert-butoxy carbonyl, p-methoxybenzyloxy carbonyl, benzhydryloxy carbonyl, benzhydryloxy carbonyl, 9-anthrylmethoxy carbonyl, 1-methyl-1-(4-biphenylyl) ethoxy carbonyl, 1-adamantyloxy carbonyl, trityl, etc.,) as well as to protected hydroxyls (for example, hydroxyls protected by methoxy methyl, tert-butoxy methyl, 2-tetrahydropyranyl, 4-methoxy-4-tetrahydropyranyl, 2-tetrahydropyranyl, 2-tetrahydrofuranyl, trityl, etc.). Desirable examples of acids that are used include organic acids (for example, formic acid, trifluoroacetic acid, benzene sulfonic acid, p-

toluene sulfonic acid), and inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid).

The method based on reduction is applied to deprotection of protected aminos (for example, aminos protected by trichloro acetyl, trifluoro acetyl, o-nitrophenyl acetyl, 2,2,2-trichloroethoxy carbonyl, benzyloxy carbonyl, p-nitrobenzyloxy carbonyl, 2,4-dichlorobenzyloxy carbonyl, isonicotinyloxy carbonyl, trityl, etc.), deprotection of protected hydroxyls (for example, hydroxyls protected by benzyl, p-nitrobenzyl), and deprotection of protected carboxyls (for example, carboxyls protected by benzyloxy methyl, benzyl, p-nitrobenzyl, phenacyl, 2,2,2-trichloro ethyl, benzhydryl, etc.). Desirable examples of reduction methods include reduction by sodium borohydride, reduction by zinc/acetic acid, and contact reduction.

The method based on ultraviolet irradiation is used in deprotection of hydroxyls and carboxyls protected by o-nitrobenzyl, for example.

The method based on hydrazine is used, for example, in deprotection of aminos protected by phthaloyls (for example, phthalimides).

The method based on phenyl hydrazine is used in deprotection of aminos protected by acetacetyl, for example.

The method based on N-methyl dithio sodium carbamate is used in deprotection of aminos and hydroxyls protected chloroacetyls, for example.

The method based on tetrabutyl ammonium fluoride is used as a method of removing protecting groups from 2-trimethylsilyl ethylcarbamate, silyl ethers, and silyl esters to yield aminos, hydroxyls, and carboxyls, respectively.

The method based on mercurous chloride is used in the deprotection of hydroxyls protected by methylthio methyl, for example.

The method based on Lewis acids is used in the deprotection of hydroxyls protected by 2-methoxyethoxy methyl, for example. Desirable examples of Lewis acids used include mercurous bromide and titanium tetrachloride.

(Preparation of medicinal compositions)

The common method of preparing medicinal compositions pursuant to the present invention is presented below. Veterinary medicine compositions, topical medicines, fisheries medicine, food compositions and cosmetic compositions can be produced by known preparation methods.

Compounds pursuant to the present invention may be blended with pharmacologically permissible carriers and administered orally or non-orally in the form of solids such as tablets, capsules, granules, powdered medicine, powder, suppositories, or in the form of liquids such as

syrups, injections, suspensions, solutions, sprays. Pharmacologically permissible carriers include excipients, lubricants, binders, disintegrating agents, disintegration inhibitors, absorbefacients, adsorbents, moisturizers, dissolution promotors, and stabilizers in solid drug products as well as solvents, dissolution promotors, isotonic agents, buffer agents, and soothing agents in liquid drug products. In addition, drug product additives such as preservatives, antioxidants, coloring agents, and sweeteners may be used as required. Furthermore, substances having immunopotentiating effects in addition to compounds represented by aforementioned general formula (I), salts or hydrates thereof may be blended in the compositions pursuant to the present invention. Methods of non-oral administration include intravenous injection, intramuscular injection, naso-gastric administration, as well as administration via the rectum, vagina or skin.

Excipients among solid drug products include glucose, lactose, sucrose, D-mannitol, crystalline cellulose, starch, calcium carbonate, light anhydrous silicic acid, sodium chloride, kaolin and urea.

Lubricants in solid drug products include magnesium stearate, calcium stearate, boric acid powder, colloidal silicic acid, talc and polyethylene glycol.

Binders in solid drug products include water, ethanol, propanol, saccharose, D-mannitol, crystalline cellulose, dextrin, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, starch solution, gelatin solution, polyvinyl pyrrolidone, calcium phosphate, potassium phosphate, and shellac.

Examples of disintegrating agents in solid drug products include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, gelatin powder, laminaran powder, croscarmellose sodium, sodium carboxymethyl starch, sodium alginate, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty-acid ester, sodium lauryl sulfate, starch, monoglyceride stearic acid, lactose and sodium cellulose glycolate.

Hydrogenated oil, saccharose, stearate, cacao butter and hydrogenated oil are desirable examples of disintegration inhibitors in solid drug products.

Quaternary ammonium salts and sodium lauryl sulfate are examples of absorbefacients in solid drug products.

Starch, lactose, kaolin, bentonite and colloidal silicic acid are examples of adsorbents in solid drug products.

Glycerol and starch are examples of moisturizers in solid drug products.

Arginine, glutamic acid, and aspartic acid are examples of dissolution promotors in solid drug products.

Human serum albumin and lactose are examples of stabilizers in solid drug products.

Tablets or capsules that are prepared as solid drug products may be coated by a gastrosoluble or enterosoluble substance (saccharose, gelatin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose phthalate) as required. Tablets with a conventional coating as required include sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film coated tablets as well as double-layered tablets or multi-layered tablets. Capsules include hard capsules and soft capsules. Higher alcohol, higher alcohol esters as well as hemisynthesized glycerides may be added in addition to aforementioned additives when forming suppositories.

Desirable examples of solvents in liquid drug products include parenteral water, alcohol, propylene glycol, macrogols, sesame oil and corn oil.

Desirable examples of dissolution promotors in liquid drug products include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanol amine, sodium carbonate and sodium citrate.

Desirable examples of suspension agents in liquid drug products include such surfactants as stearyl triethanol amine, sodium lauryl sulfate, lauraminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate, and such hydrophilic polymers as polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, and hydroxypropyl cellulose.

Desirable examples of isotonic agents in liquid drug products include sodium chloride, glycerol, and D-mannitol.

Desirable examples of buffer agents in liquid drug products include phosphates, acetates, carbonates and citrates.

Desirable examples of soothing agents in liquid drug products include benzyl alcohol, benzalkonium chloride, and procaine hydrochloride.

Desirable examples of preservatives in liquid drug products include paraoxybenzoic acid esters, chlorobutanol, benzyl alcohol, 2-phenylethyl alcohol, dehydroacetic acid, and sorbic acid.

Desirable examples of antioxidants in liquid drug products include sulfites, ascorbic acid, α-tocopherols and cysteine.

Sterilization of liquids and suspensions is desirable in preparing injections, and such injections should be isotonic with blood. Usually, these are sterilized by filtration using bacteria-retaining filters, by blending disinfectants or by irradiation. After such treatment, these may be solidified by such methods as freeze drying, followed by the addition of sterile water or sterile injection diluent (lidocaine hydrochloride solution, physiological saline solution, glucose solution, ethanol or mixtures of these) immediately before use.

As required, medicinal compositions may also contain coloring agents, preservatives, flavors and fragrances, flavor enhancers, sweeteners as well as other drugs.

(Immunopotentiation method)

The immunopotentiation method pursuant to the present invention is a method of activating the immunity of a subject of examination that includes the step of administering aforementioned compositions pursuant to the present invention to said subject of examination. The administration route, the carriers used in administration, and the types of drug products are as stated above pursuant to preparation of medicinal compositions.

The subject of examination discussed here connotes humans or animals other than humans. The animals may be mammals or non-mammalian animals. Fish are permissible, for example.

The amount of active ingredient that is administered varies with the disease state, the administration route, each patient=s age and weight, but the oral dosage to adults would usually be in the range of 0.1 to 100 mg/kg/day, preferably the range of 1 to 50 mg/kg/day.

(Drug sensitivity restorative agents)

Compounds represented by general formula (I) and salts thereof, especially compounds represented by formula (M) below and salts thereof have drug sensitivity restorative effects. In short, the present invention concerns drug sensitivity restorative agents that contain compounds represented by general formula (I) and salts thereof.

The term "drug sensitivity restorative agents" used here connotes substances that restore drug sensitivity to drug resistant pathogenic microorganisms. The drug sensitivity restorative agents pursuant to the present invention are outstanding in their restoration of drug sensitivity especially to Pseudomonas with reduced drug sensitivity due to OprM overproduction.

Various types of antibiotics that can be used jointly with drug sensitivity restorative agents in the present invention are stated in the working examples discussed below. Examples of antibiotics that can be used in addition to the antibiotics used in the working examples include β-lactam antibiotics such as CZOP and piperacillin (PIPC) as well as carbapenem antibiotics such as meropenem (MEPM).

"OprM" is one of numerous Pseudomonas efflux pumps that bring about drug resistance of Pseudomonas. Concretely, "OprM" that is coded on the Pseudomonas chromosome induces high expression of the drug efflux pump (MexAB-OprM) coded on chromosomes through mutation of the naIB gene locus on the chromosome.

OprI and OprN are other Pseudomonas efflux pumps that induce Pseudomonas drug resistance in addition to OprM.

Pharmaceutical compositions having outstanding antibacterial properties through combination of various types of antibiotics and drug sensitivity restorative agents pursuant to the present invention are provided in this manner.

(Method of drug sensitivity restoration)

The method of drug sensitivity restoration pursuant to the present invention is a method of restoring sensitivity of subjects of examination to drugs that contains the step of administering the drug sensitivity restorative agents pursuant to the present invention to said subjects of examination.

The administration route, the carriers used in administration, and the types of drug products are as stated above pursuant to preparation of medicinal compositions.

The subject of examination discussed here connotes humans or animals other than humans. The animals may be mammals or non-mammalian animals. Fish are permissible, for example.

The amount of active ingredient that is administered varies with the disease state, the administration route, each patient=s age and weight, but the oral dosage to adults would usually be in the range of 0.1 to 100 mg/kg/day, preferably the range of 1 to 50 mg/kg/day.

(Working Examples)

The present invention as well as its efficacy are explained in detail below through working examples (including drug product examples) and trial examples, but the present invention is not restricted to these.

(Working Example 1)

Synthesis of 2-benzyloxy-2'-(3,5-dimethoxyphenoxy) acetophenone (A-56)

1) Synthesis of 2-benzyloxybromobenzene

Benzyl bromide (1.0 ml, 8.4 mmol) was added at room temperature under stirring to a suspension comprising 2-bromophenol (1.0 g, 5.8 mmol), potassium carbonate (4.0 g, 29 mmol), and N,N-dimethyl formamide (5.0 ml). After stirring for 5.8 hours, diethyl ether was added to the reaction mixture, followed by sequential washing with water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate, followed by solvent removal under vacuum and purification by silica gel column chromatography (n-hexane-5% diethyl ether/n-hexane) to yield 2-benzyloxybromobenzene (1.5 g, 99%) target material.

^{1}H-NMR (d ppm, $CDCl_3$/TMS) : 5. 1 5 (2H, s), 6.84 (1H, dt, J=1.4, 7.8), 6.93 (1H, dd, J=8.3, 1.4), 7.19-7.49 (6H, m), 7.56 (1H, dd, J =7.8, 1.7).

2) Synthesis of 2-(3,5-dimethoxyphenoxy)-N-methoxy-N-methyl acetamide

Bromoethyl acetate (1.5 ml, 13 mmol) was added at room temperature under stirring to a suspension comprising 3,5-dimethoxyphenol (1.5 g, 9.7 mmol), potassium carbonate (4.0 g, 29 mmol), and N,N-dimethyl formamide (10 ml). After stirring for 3 hours, ethyl acetate-diethyl ether (1:1) was added to the reaction mixture, followed by sequential washing with water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate, followed by solvent removal under vacuum to yield crude 2-(3,5-dimethoxyphenoxy) ethyl acetate.

The resulting 2-(3,5-dimethoxyphenoxy) ethyl acetate was dissolved in ethanol (10 ml) without purification followed by the addition of 1N-sodium hydroxide solution (13 ml, 13 mmol) at room temperature and stirring for 2 hours. The reaction mixture was rendered acidic with 5% potassium hydrogensulfate aqueous solution and was then extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with anhydrous sodium sulfate. The solvent was then removed under vacuum to yield crude 2-(3,5-dimethoxyphenoxy) acetic acid.

N,O-dimethyl hydroxylamine hydrochloride (1.1 g, 11 mmol), N,N-dimethylformamide (20 ml), and triethyl amine (3.4 ml, 24 mmol) were added to unpurified 2-(3,5-dimethoxyphenoxy) acetic acid, followed by the addition of cyano diethyl phosphate (1.9 ml, 13 mmol) and stirring for 14.5 hours at room temperature. More cyano diethyl phosphate (0.3 ml, 2 mmol) was added and stirred for 4.5 hours, followed by the addition of ethyl acetate-diethyl ether (1:1) and sequential washing with water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate, followed by solvent removal under vacuum. The residue was purified by silica gel column chromatography (30% ethyl acetate/n-hexane-50% ethyl acetate/ n-hexane) to yield 2-(3,5-dimethoxyphenoxy)-N-methoxy-N-methyl acetamide (2.3 g, 93%) target material.

^{1}H-NMR (d ppm, $CDCl_3$/TMS): 3.23 (3H, s), 3.75 (3H, s), 3.76 (6H, s), 4.77 (2H, s), 6.11 (1H, t, J=2.1), 6.14 (2H, d, J=2.1).

3) Synthesis of 2-benzyloxy-2'-(3,5-dimethoxyphenoxy) acetophenone

2-benzyloxybromobenzene (1.6 g, 6.1 mmol) was dissolved in tetrahydrofuran (5 ml), followed by the addition of magnesium (180 mg, 7.5 mmol) and ethyl iodide (0.05 ml, 0.6 mmol) at room temperature. Stirring for 1 hour at 50^{0}C was followed by cooling to prepare Grignard reagent. The resulting Grignard reagent was cooled with dry ice-acetone followed by dropwise addition to a cooled tetrahydrofuran solution (5 ml) of 2-(3,5-dimethoxyphenoxy)-N-methoxy-N-methyl acetamide (1.7 g, 6.7 mmol), continued stirring for 1.5 hours at room temperature, and ice cooling. 1N-hydrochloric acid (20 ml) was added to the reaction mixture and stirred, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried with anhydrous magnesium sulfate, followed by solvent removal under vacuum. Diethyl ether was added to the resulting crude product to yield target material through filtration of crystals (1.6 g, 70%).

Melting point: 107-108^{0}C

^{1}H-NMR (d ppm, $CDCl_3$,/TMS): 3.71 (6H, s), 5.11 (2H, s), 5.19 (2H, s), 5.97 (2H, d, J=2.0), 6.06 (1H, t, J=2.0), 7.06-7.10 (2H, m).7.37-7.54 (5H, m), 7.52 (1H, dt, J=1.8, 7.9), 7.95 (1H, dd, J=7.9, 1.8)

Compound of formula (I-A) was synthesized by essentially the same method except for modification of specific substituents. The compound numbers of the synthesized compounds and the physical properties are presented in Table 12.

(Working Example 2)

Synthesis of 2-(2-benzyloxyphenyl)-3-(3,5-dimethoxyphenoxy) propane (B-58)

Tetrahydrofuran (6 ml) was added to methyl triphenyl phosphonium iodide (800 mg, 2.0 mmol), followed by the dropwise addition of 0.5M potassium hexamethyl disilazane toluene solution (3.7 ml, 1.9 mmol) under stirring at room temperature. Stirring for 20 minutes was followed by the addition of a tetrahydrofuran solution of 2-benzyloxy-2'-(3,5-dimethoxyphenoxy) acetophenone (500 mg, 1.3 mmol) (7 ml). Stirring for another 1.4 hours was followed by the addition of saturated ammonium chloride solution to the reaction mixture and extraction with ethyl acetate. The organic layer was washed with saturated brine and dried with anhydrous magnesium sulfate, followed by solvent removal under vacuum. The resulting crude product was purified by silica gel column chromatography (20% ethyl acetate/n-hexane) to yield 2-(2-benzyloxyphenyl)-3-(3,5-dimethoxyphenoxy) propane (436 mg, 88%) oily material.

^{1}H-NMR (d ppm, $CDCl_3$,/TMS):3.71 (6H, s), 4.87 (2H, s), 5.09 (2H, s), 5.32 (1 H, br), 5.50 (1H, br), 6.06 (1 H, t, J=2.2), 6.09 (2H, d, J=2.2), 6.93 (1H, d, J=8.1), 6.96 (1 H, t, J=7.3), 7.23-7.38 (7H, m).

Compound of formula (I-B) was synthesized by essentially the same method except for modification of specific substituents. The compound numbers of the synthesized compounds and the physical properties are presented in Table 12.

(Working Example 3)

Synthesis of 3-(2-acetoxy-4,6-dimethoxyphenyl)-2-(2-benzyloxyphenyl) propane (C-15)

Sodium acetate (650 mg, 7.9 mmol) and acetic anhydride (16 ml, 170 mmol) were added to 2-(2-benzyloxyphenyl)-3-(3,5-dimethoxyphenoxy) propane (300 mg, 0.80 mmol), followed by stirring for 1 hour at 210^{0}C in a nitrogen atmosphere in a pressure-proof sealed tube. Water was added to the reaction mixture after cooling, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried with anhydrous magnesium sulfate, followed by solvent removal under vacuum. The resulting crude material was purified by silica gel column chromatography (n-hexane-10% ethyl acetate/ n-hexane) to yield 3-(2-acetoxy-4,6-dimethoxyphenyl)-2-(2-benzyloxyphenyl) propane (250 mg, 75%) oily material.

^{1}H-NMR (d ppm, $CDCl_3$,/TMS):2.04 (3H, s), 3.62 (3H, s), 3.68 (2H, s), 3.76 (3 H, s), 4.85 (1H, br), 4.98 (1H, br), 5.11 (2H, s), 6.22 (1H, d, J=2.2), 6.31 (1H, d, J=2.2), 6.89 (1H, t, J=7.3), 6.92 (1H, d, J=8.5), 7.11 (1H, d, J=7.3), 7.20 (1H, ddd, J=8.5, 7.3, 2.0), 7.31 (1H, t, J=7.3), 7.37 (2H, t, J=7.3), 7.46 (2H, d, J=7.3).

Compound of formula (I-C) was synthesized by essentially the same method except for modification of specific substituents. The compound numbers of the synthesized compounds and the physical properties are presented in Table 12.

(Working Example 4)

Synthesis of 2-(2-benzyloxyphenyl)-3-(2,4-dimethoxy-6-hydroxyphenyl)-1-propanol (D-13)

A solution of 0.5M 9-borobicyclo [3.3.1] nonanetetrahydrofuran (9.0 ml, 4.5 mmol) was added to 3-(2-acetoxy-4,6-dimethoxyphenyl)-2-(2-benzyloxyphenyl) propane (190 mg, 0.45 mmol) and dissolved, followed by stirring for 16.7 hours at room temperature and ice cooling. Water (4.5 ml), methanol (15 ml), 30% hydrogen peroxide solution (2.0 ml), and 10% sodium hydroxide solution (2.0 ml) were added to the reaction mixture. Stirring for 10 minutes was followed by stirring for another two hours at room temperature, further addition of water, and extraction with ethyl acetate. The organic layer was washed with saturated brine and dried with anhydrous magnesium sulfate, followed by solvent removal under vacuum. The resulting crude product was purified by silica gel column chromatography (10% ethyl acetate/n-hexane-30% ethyl acetate/n-hexane) to yield 2-(2-benzyloxyphenyl)-3-(2,4-dimethoxy-6-hydroxyphenyl)-1-propanol (150 mg, 84%) oily material.

^{1}H-NMR (d ppm, $CDC1_3$/TMS):2.84 (1 H, dd, J=14.2, 3.9), 2.88 (1H, br), 3.11 (1H, dd, J=14.2, 11.1), 3.41 (1H, m), 3.66 (3H, s), 3.70 (1H, dd, J=11.5, 4.6), 3.74 (3H, s), 3.82 (1H, dd, J=11.5, 2.9), 5.13 (2H, s), 6.05 (1 H, d, J=2.4), 6.12 (1H, d, J=2.4), 6.95-6.99 (2H, m), 7.20 (1H, ddd, J=8.1, 7.3, 1.7), 7.29-7.43 (6H, m), 7.51 (1H, br).

Compound of formula (I-D) was synthesized by essentially the same method except for modification of specific substituents. The compound numbers of the synthesized compounds and the physical properties are presented in Table 12.

(Working Example 5)

Synthesis of 3-(2-benzyloxyphenyl)-3,4-dihydro-5,7-dimethoxy-2H-1-benzopyran (E-76)

Triphenylphosphine (280 mg, 1.1 mmol) was added to 2-(2-benzyloxyphenyl)-3-(2,4-dimethoxy-6-hydroxyphenyl)-1-propanol (145 mg, 0.37 mmol) and then dissolved in tetrahydrofuran (7.4 ml), followed by dropwise addition of diethylazodicarboxylate (0.17 ml, 1.1 mmol) under stirring at room temperature. Stirring was then continued at room temperature followed by removal of solvent under vacuum. This was purified by silica gel column chromatography (n-hexane-10%

diethyl ether/n-hexane) followed by crystallization from hexane to yield 3-(2-benzyloxyphenyl)-3,4-dihydro-5,7-dimethoxy-2H-1-benzopyran (79 mg, 57%) target material. Melting point: 120 to 121^{0}C

^{1}H-NMR (d ppm, $CDCl_3$/TMS):2.74 (1H, dd, J=16.5, 10.4), 2.95 (1H, ddd, J=16.5, 5.9, 2.0), 3.71 (IH, m), 3.77 (3H, s), 3.78 (3H, s), 4.04 (1H, dd, J=10.2, 9.8), 4.33 (1H, ddd, J=10.2, 3.3, 1.8), 6.08 (2H, s), 6.92-6.96 (2H, m), 7.16-7.23 (2H, m), 7.29-7.42 (5H, m).

Compound of formula (I-E) was synthesized by essentially the same method except for modification of specific substituents. The compound numbers of the synthesized compounds and the physical properties are presented in Table 12.

(Working Example 6)

Synthesis of 3-(2-benzyloxyphenyl)-2,3-dihydro-4,6-dimethoxy-3-methylbenzofuran (F-35)

2-(2-benzyloxyphenyl)-3-(3,5-dimethoxyphenoxy) propane (69 mg, 0.18 mmol) was dissolved in dichloromethane (10 ml), followed by the addition of boron trifluoride diethyl ether complex (0.05 ml, 0.39 mmol) at room temperature under stirring and further stirring for 24 hours. Saturated sodium hydrogencarbonate solution was added to the reaction mixture and the dichloromethane was extracted. The organic layer was dried with anhydrous magnesium sulfate, followed by solvent removal under vacuum. The resulting crude product was applied to silica gel column chromatography (n-hexane-10% diethyl ether/n-hexane) to yield target material containing a slight amount of impurities (37 mg, 54%). Purification was continued via HPLC (silica gel column, 5% diethyl ether/ n-hexane) to yield crystals of 3-(2-benzyloxyphenyl)-2,3-dihydro-4,6-dimethoxy-3-methylbenzofuran target material from diethyl ether-n-hexane. melting point: 117-118^{0}C

^{1}H-NMR (d ppm, $CDCl_3$/TMS): 1.85 (3H, s), 3.76 (3H, s), 3.78 (3H, s), 4.46 (1H, d, J=9.0), 4.86 (1H, d, J=9.0), 5.08 (1H, d, J=11.7), 5.11 (1H, d, J=11.7), 6.04 (1H, d, J=2.0), 6.10 (1H, d, J=2.0), 6.83 (1 H, dt, J=1.1, 7.6), 6.95 (1H, dd, J=8.1, 1.1), 7.00 (1H, dd, J=7.6, 1.7), 7.18 (1H, ddd, J=8.1, 7.6, 1.7), 7.32-7.40 (5H, m).

Compound of formula (I-F) was synthesized by essentially the same method except for modification of specific substituents. The compound numbers of the synthesized compounds and the physical properties are presented in Table 12.

(Working Example 7)

Synthesis 2-(2-benzyloxyphenyl)-2,3-dihydro-4,6-dimethoxy-2-methylbenzofuran (H-11)

3-(2-acetoxy-4,6-dimethoxyphenyl)-2-(2-benzyloxyphenyl) propane (55 mg, 0.13 mmol) was dissolved in a mixed solution of tetrahydrofuran (1.3 ml) and methanol (1.3 ml), followed by the addition of 1N sodium hydroxide solution (0.2 ml, 0.2 mmol) and stirring for 16.5 hours at room

temperature to yield 2-(2-benzyloxyphenyl)-3-(2,4-dimethoxy-6-hydroxyphenyl) propane. The reaction mixture was subsequently chilled in ice without further treatment, followed by the addition of 0.5M methanol sulfate solution (1.5 ml, 0.75 mmol) and stirring for 4 hours at room temperature. The reaction mixture was again chilled with ice, followed by the addition of concentrated sulfuric acid (0.04 ml, 0.75 mmol) and gradual heating to 60^0C. Stirring for 14 hours at 60^0C was followed by air cooling, the addition of saturated sodium hydrogencarbonate solution to render it basic, and extraction with ethyl acetate. The organic layer was washed with saturated brine and dried with anhydrous magnesium sulfate, followed by solvent removal under vacuum. The resulting crude product was purified by silica gel column chromatography (n-hexane-10% ethyl acetate/n-hexane) to yield 2-(2-benzyloxyphenyl)-2,4-dihydro-4,6-dimethoxy-2-methyl benzofuran (45 mg, 91%) target material as oily material. Part was crystallized from n-hexane and the melting point was measured. melting point 63-64^{0}C

^{1}H-NMR (d ppm, $CDCl_3$/TMS) :1.81 (3H, s), 3.30 (1H, d, J=15.6), 3.38 (1 H, d, J=15.6), 3.73 (3H, s), 3.77 (3H, s), 5.13 (2H, s), 5.97 (1H, d, J=2.0), 6.17 (1H, d, J=2.0), 6.92-6.96 (2H, m), 7.21 (1H, ddd, J=8.1, 7.3, 1.7), 7.31-7.45 (5H, m), 7.65 (1H, dd, J =7.8, 1.7).

Compound of formula (I-H) was synthesized by essentially the same method except for modification of specific substituents. The compound numbers of the synthesized compounds and the physical properties are presented in Table 12.

(Working Example 8)

Synthesis of 5-methoxy-3-p-tolyl-2H-1-benzopyran (J-16)

1) Method of synthesizing 3-cyano-5-methoxy-2H-1-benzopyran

2-hydroxy-6-methoxybenzaldehyde (9.13 g, 0.06 mmol) was dissolved in acrylonitrile (16.0 g, 0.30 mmol), followed by the addition of 1,4-diazabicyclo [2.2.2] octane (1.68 g, 0.015 mmol) and heated stirring for 48 hours at 85^0C. Cooling to room temperature was followed by the addition of ethyl acetate and sequential washing with 1N-sodium hydroxide solution, 1N-hydrochloric acid, and saturated brine. This was then dried with magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (n-hexane: ethylacetate=3:1) to yield 3-cyano-5-methoxy-2H-1-benzopyran (6.36 g, 57%) colorless crystals of target material.
melting point: 66^0C

^{1}H-NMR (d ppm, $CDC1_3$/TMS) :3.85 (3H, s), 4.74 (2H, d, J=1.3), 6.46-6.52 (2H, m), 7.21 (1H, t, J=8.2), 7.54 (1H, t, J=1.3).

2) Synthesis of 3-carboxy-5-methoxy-2H-1-benzopyran

3-cyano-5-methoxy-2H-1-benzopyran (6.23 g, 0.033 mmol) was suspended in 10% sodium hydroxide solution (100 ml, 0.25 mmol) followed by heated reflux for 22 hours. This was cooled

to room temperature followed by the dropwise addition of concentrated hydrochloric acid to render it acidic. The precipitated crystals were then filtered, washed with water and dried under vacuum at 75°C to yield 3-carboxy-5-methoxy-2H-1-benzopyran (6.80 g, 100%) target material as colorless powder.

^{1}H-NMR (δ ppm, DMSO-d_6/TMS): 3.83 (3H, s), 4.84 (2H, d, J=1.0), 6.48 (1 H, d, J=8.2), 6.62 (1H, d, J=8.2), 7.24 (1 H, t, J=8.2), 7.57 (1H, brs).

3) Synthesis of 3,4-dihydro-5-methoxy-2H-1-benzopyran-3-on

3-carboxy-5-methoxy-2H-1-benzopyran (7.22 g, 0.035 mmol) and triethylamine (5.6 ml, 0.040 mmol) were dissolved in anhydrous dichloromethane (70 ml), followed by the dropwise addition of a solution of diphenylphosphoryl azide (9.63 g, 0.035 mmol) in anhydrous toluene (28 ml) at 50°C, followed by the addition of anhydrous toluene (70 ml) at 60°C. Heating for 1.5 hours at 85°C was followed by the dropwise addition of 6N-hydrochloric acid (56 ml) and heated reflux for 2 hours. Cooling to room temperature was followed by the addition of water and ethyl acetate and washing of the separated organic layer with saturated brine. Drying with magnesium sulfate was followed by concentration. The residue was purified by silica gel column chromatography (n-hexane: ethyl acetate=3:1) to yield 3,4-dihydro-5-methoxy-2H-1-benzopyran-3-on (5.34 g, 85%) target material as pale-yellow oil.

^{1}H-NMR (d ppm, $CDC1_3$/TMS) : 3.55 (2H, s), 3.83 (3H, s), 4.39 (2H, s), 6.59 (1 H, d, J=8.2), 6.68 (1H, d, J=8.2), 7.18 (1 H, t, J=8.2).

4) Synthesis of 5-methoxy-3-trifluoromethane sulfoxy-2H-1-benzopyran

3,4-dihydro-5-methoxy-2H-1-benzopyran-3-on (35.7 mg, 2 mmol) was dissolved in anhydrous dichloromethane (4 ml) followed by the dropwise addition of diisopropyl ethyl amine (0.39 ml, 2.24 mmol) and anhydrous trifluoromethane sulfonic acid (0.35 ml, 2.08 mmol) under cooling at -78°C. Stirring for 1.5 hours at that temperature was followed by the addition of ice water, extraction with ethyl acetate and washing with saturated brine. This was then dried with magnesium sulfate and concentrated. 5-methoxy-3-trifluoromethane sulfoxy-2H-1-benzopyran (645 mg) was derived as crude product.

^{1}H-NMR (d ppm, $CDC1_3$/TMS) :3.84 (3H, s), 4.81 (2H, d, J=1.0), 6.50 (1H, d, J=8.3), 6.51 (1H, d, J=8.3), 6.83 (1 H, brs), 7.13 (1H, t, J=8.3).

5) Synthesis of 5-methoxy-3-p-tolyl-2H-1-benzopyran

5-methoxy-3-trifluoromethane sulfoxy-2H-1-benzopyran (645 mg) was dissolved in toluene (4 ml) and ethanol (4 ml), followed by the addition of methylphenyl boronic acid (287 mg, 2.11 mmol), 2M-sodium carbonate solution (4 ml) and palladium tetrakistriphenyl phosphine (1.16 mg, 0.1 mmol). This was subjected to heated reflux for 3 hours in a nitrogen stream and cooled to room temperature, followed by the addition of 1N-hydrochloric acid and ethyl acetate. The

reaction product was filtered out at a high flow. The separated organic layer was washed with saturated sodium bicarbonate and saturated brine. It was then dried with magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate:25:1) to yield 5-methoxy-3-p-tolyl-2H-1-benzopyran (226 mg, 45%) target material as colorless crystals. melting point: 86-87^{0}C

^{1}H-NMR (d ppm, $CDC1_3$/TMS) :2.36 (3H, s), 3.86 (3H, s), 5.10 (2H, d, J=1.3), 6.48 (1 H, dd, J=0.8, 8.2), 6.52 (1H, dd, J=0.8, 8.2), 7.07 (1H, t, J=8.2), 7.15 (1H, brs), 7.18 (2H, d, J=8.2), 7.37 (2H, d, J=8.2)

Compound of formula (I-J) was synthesized by essentially the same method except for modification of specific substituents. The compound numbers of the synthesized compounds and the physical properties are presented in Table 12.

(Working Example 9)

Synthesis of 3,4-dihydro-5-methoxy-3-p-tolyl-2H-1-benzopyran (E-13)

5-methoxy-3-p-tolyl-2H-1-benzopyran (127 mg, 0.503 mmol) was dissolved in methanol (2 ml) and dichloromethane (2 ml), followed by the addition of 10% palladium carbon (21.3 mg). Stirring for 5.5 hours under a hydrogens stream of one atmosphere at room temperature was followed by high-flow filtration of the reaction product. Concentration was followed by purification of the residue by silica gel column chromatography (n-hexane: ethyl acetate = 8:1) to yield 3,4-dihydro-5-methoxy-3-p-tolyl-2H-1-benzopyran (118 mg, 92%) target material as colorless crystals. melting point: 99-101^{0}C

^{1}H-NMR (d ppm, $CDC1_3$/TMS) :2.34 (3H, s), 2.74 (1H, dd, J=11.2, 16.8), 3.07 (1H, ddd, J=2.0, 5.2, 16.8), 3.11-3.20 (1H, m), 3.81 (3H, s), 3.96 (1H, t, J=10.4), 4.31 (1H, ddd, J=2.0, 3.6, 10.4), 6.45 (1H, d, J=8.0), 6.53 (1H, d, J=8.0), 7.08 (1H, t, J=8.0), 7.16 (4H, s).

(Working Example 10)

Synthesis of 2-(2-benzyloxyphenyl)-4,6-dimethoxybenzofuran (K-37)

1) Synthesis of 2-(3,5-dimethoxyphenoxy) acetaldehyde dimethyl acetal

3,5-dimethoxyphenol (15.42 g, 0.1 mmol) was dissolved in DMF (50 ml), followed by the addition of 2-bromoacetaldehyde dimethyl acetal (20.28 g, 0.12 mmol), potassium carbonate (20.73 g, 0.15 mmol), and potassium iodide (0.1 g), and heated stirring at 140^{0}C for 18 hours. This was cooled to room temperature followed by the addition of water, extraction with diethyl ether, washing of the organic layer with water and saturated brine, drying with anhydrous magnesium sulfate, and concentration under vacuum. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=5:1) to yield 2-(3,5-dimethoxyphenoxy) acetaldehyde dimethyl acetal (22.6 g, 93%) target material as colorless oily material.

^{1}H-NMR (d ppm, $CDC1_3$/TMS):3.45 (6H, s), 3.76 (6H, s), 3.97 (2H, d, J=5.3), 4.71 (1H, t, J=5.3), 6.11 (3H, m).

2) Synthesis of 4,6-dimethoxy benzofuran

2-(3,5-dimethoxyphenoxy) acetaldehyde dimethyl acetal (21.0 g, 86.7 mmol) was dissolved in toluene (100 ml), followed by the addition of pyridinium p-toluene sulfonate (21.78 g, 86.7 mmol). A Dean-Stark draining tube was attached and reflux was conducted for 24 hours, followed by the addition of water and diethyl ether and filtration removal of the precipitating solid. The filtrate was extracted with diethyl ether, after which the organic layer was washed with water and saturated brine, dried with anhydrous magnesium sulfate and concentrated under vacuum. Hexane was added to the concentrated liquid and the precipitated solid was filtered off, followed by concentration under vacuum of the filtrate. The residue was purified by silica gel column chromatography (n-hexane: ethyl acetate=10:1) to yield 4,6-dimethoxy benzofuran (3.32 g, 21%) target material as colorless oily material.

^{1}H-NMR (d ppm, $CDC1_3$/TMS): 3.84 (3H, s), 3.90 (3H, s), 6.33 (1 H, d, J=1.8), 6.66 (1 H, dd, J=1.8, 1.0), 6.77 (1H, dd, J=2.2, 1.0), 7.44 (1H, d, J=2.2).

3) Synthesis of 4,6-dimethoxy-2-benzofuran boronic acid

In a nitrogen stream, 4,6-dimethoxybenzofuran (3.43 g, 19.2 mmol) was dissolved in THF (20 ml) and then cooled in a dry ice-acetone bath at -78^{0}C. N-butyl lithium (12.6 ml, 1.53 M hexane solution, 19.2 mmol) was dropwise added, followed by stirring for 2 hours at room temperature, the addition of THF (20 ml), and stirring for 0.5 hours at room temperature. The reaction mixture was dropwise added at -78^{0}C into a 40 ml THF solution of triisopropyl borate (3.62 g, 19.2 mmol), stirred for 1.5 hours at -78^{0}C and then stirred for 0.5 hour at room temperature. Under ice cooling, 5% sulfuric acid (20 ml) was added, followed by stirring for 2 hours at room temperature and extraction with ethyl acetate. The organic layer was washed with water and saturated brine, dried with anhydrous magnesium sulfate, then concentrated under vacuum. The resulting residue was suspended in diethyl ether and filtered to yield 1.04 g of target material as brown powder solid. The filtrate was concentrated under vacuum, after which the residue was dissolved in an ethyl acetate-diethyl ether mixed solution. This was then extracted with 1N-sodium hydroxide. The aqueous layer was rendered acidic with 20% sulfuric acid, followed by extraction with ethyl acetate. The organic layer was washed with water and saturated brine, dried with anhydrous magnesium sulfate, and the solvent was removed under vacuum. The residue was suspended in diethyl ether and the solid was filtered off. The filtrate was concentrated under vacuum, followed by suspension of the solid in diethyl ether and filtration repeated three times to yield 1.66 g of 4,6-dimethoxy-2-benzofuran boronic acid in the form of brown powder solid target material (total yield of 2.70 g, 63%).

^{1}H-NMR (d ppm, $CDC1_3$+DMSO-d_6/TMS): 3.84 (3H, s), 3.90 (3H, s), 6.28 (1H, d, J=2.0), 6.65 (1H, t, J=1.0), 6.69 (2H, s), 7.43 (1H, d, J=1.O).

4) Synthesis of 2-(2-benzyloxyphenyl)-4,6-dimethoxybenzofuran

1,2-dimethoxy ethane (7.2 ml), ethanol (3.6 ml), and 2N-sodium carbonate solution (3.6 ml) were dissolved in 4,6-dimethoxy-2-benzofuran boronic acid (200 mg, 0.9 mmol) and 2-benzyloxy bromobenzene (237 mg, 0.9 mmol). Air was purged from the system and displaced by nitrogen, followed by the addition of tetrakis (triphenylphosphine) palladium (0) (52 mg, 0.045 mmol) and reflux for 3 hours. Cooling was followed by the addition of water and filtration of the reaction mixture using cellite. This was then washed with diethyl ether. The filtrate was combined with wash and concentrated under vacuum, followed by extraction of the residue with diethyl ether, washing with water and saturated brine, drying with anhydrous magnesium sulfate, and solvent removal under vacuum. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate = 10:1) to yield 2-(2-benzyloxyphenyl)-4,6-dimethoxybenzofuran (0.17 g, 52%) target material in the form of a white solid. melting point: 109-110^{0}C

^{1}H-NMR (d ppm, $CDC1_3$/TMS):3.86 (3H, s), 3.88 (3H, s), 5.29 (2H, s), 6.31 (1H, d, J=1.7), 6.70 (1H, dd, J=1.7, 1.0), 6.99 (1H, dd, J=7.6, 1.0), 7.05 (1H, dt, J=1.0, 7.6), 7.21 (1 H, dt, J=1.6, 7.6), 7.30-7.51 (5H, m), 8.00 (1H, dd, J =7.6, 1.6).

Compound of formula (I-K) was synthesized by essentially the same method except for modification of specific substituents. The compound numbers of the synthesized compounds and the physical properties are presented in Table 12.

(Table 12)

Cmpd.No.	Properties
No.	
A-47	3.70(6H, s), 4.35(2H, s), 5.81(2H, d, J=2.0), 6.04(1H, t, J=2.0), 7.35-7.45(7H, m), 7.54-7.61(2H, m)
A-56	3.71(6H, s), 5.11(2H, s), 5.19(2H, s), 5.97(2H, d, J=2.0), 6.06(1H, t, J=2.0), 7.06-7.10(2H, m), 7.37-7.54(5H, m), 7.52(1H, dt, J=1.8, 7.9), 7.95(1H, dd, J=7.9, 1.8)
A-66	mp 127-128℃
B-9	3.74(3H, s), 4.85(2H, br), 5.03(2H, s), 5.04(2H, s), 5.98(1H, br), 3.42(1H, br), 6.43-6.48(3H, m), 6.57(1H, dd, J=8.3, 2.3), 6.61(1H, d, J=2.3), 7.06(1H, m), 7.19(1H, d, J=8.3), 7.31-7.44(10H, m)
B-13	3.74(3H, s), 4.80(2H, s), 5.03(2H, s), 5.05(2H, s), 5.25(1H, q, J=1.7), 5.39(1H, q, J=1.7), 6.57 (1H, dd, J=8.3, 2.3), 6.62(1H, d, J=9.3), 6.69(2H, d, J=9.3), 6.78(2H, d, J=9.3), 7.17(1H, d, J=8.3)
B-49	mp 107-108℃
B-51	3.77(6H, s), 4.89(2H, s), 5.49(1H, d, J=0.8), 5.68(1H, d, J=0.8), 6.11(1H, t, J=2.0), 6.17(2H, d, J=2.0), 7.32-7.37(1H, m), 7.42-7.47(2H, m), 7.55(2H, d, J=8.4), 7.54-7.62(2H, m), 7.59(2H, d, J=8.4)
B-58	3.71(6H, s), 4.87(2H, s), 5.09(2H, s), 5.32(1H, br), 5.50(1H, br), 6.06(1H, t, J=2.2), 6.09(2H, d, J=2.2), 6.93(1H, d, J=8.1), 6.96(1H, t, J=7.3), 7.23-7.38(7H, m)
B-62	2.31(3H, s), 2.32(3H, s), 3.76(6H, s), 4.61(2H, s), 5.13(1H, d, J=0.8), 5.59(1H, d, J=0.8), 6.09(1H, t, J=1.6), 6.12(2H, d, J=1.6), 6.98-7.06(3H, m)
B-70	3.71(6H, s), 4.83(2H, s), 5.04(4H, s), 5.30(1H, d, J=1.2), 5.43(1H, d, J=1.2), 6.08(3H, m), 6.57(2H, m), 7.19(1H, d, J=7.9), 7.29-7.47(10H, m)
C-13	mp 106-108℃
C-15	2.04(3H, s), 3.62(3H, s), 3.68(2H, s), 3.76(3H, s), 4.85(1H, br), 4.98(1H, br), 5.11(2H, s) 6.22(1H, d, J=2.2), 6.31(1H, d, J=2.2), 6.89(1H, t, J=7.3), 6.92(1H, d, J=8.5), 7.11(1H, d, J=7.3) 7.20(1H, ddd, J=8.5, 7.3, 2.0), 7.31(1H, t, J=7.3), 7.37(2H, t, J=7.3), 7.46(2H, d, J=7.3)

(Table 12-continued)

C-19	2.23(3H, s), 2.29(3H, s), 2.30(3H, s), 3.41(2H, s), 3.72(3H, s), 3.78(3H, s), 4.77(1H, d, J=1.2), 4.80(1H, d, J=1.2), 6.26(1H, d, J=2.4), 6.34(1H, d, J=2.4), 6.91-7.00(3H, m)
D-13	2.84(1H, dd, J=14.2, 3.9), 2.88(1H, br), 3.11(1H, dd, J=14.2, 11.1), 3.41(1H, m), 3.66(3H, s), 3.70(1H, dd, J=11.5, 4.6), 3.74(3H, s), 3.82(1H, dd, J=11.5, 2.9), 5.13(2H, s), 6.05(1H, d, J=2.4), 6.12(1H, d, J=2.4), 6.95-6.99(2H, m), 7.20(1H, ddd, J=8.1, 7.3, 1.7), 7.29-7.43(6H, m), 7.51(1H, br)
E-10	2.76(1H, dd, J=10.8, 16.8), 3.09(1H, ddd, J=2.0, 5.6, 16.8), 3.15-3.24(1H, m), 3.81(3H, s), 3.99(1H, t, J=10.4), 4.34(1H, ddd, J=2.0, 3.2, 10.4), 6.45(1H, d, J=8.0), 6.54(1H, d, J=8.0), 7.09(1H, t, J=8.0), 7.24-7.39(5H, m)
E-11	mp 71-72℃
E-13	mp 99-101℃
E-14	mp 63-64℃
E-22	mp 118-121℃
E-24	mp 109-110℃
E-37	2.96(1H, dd, J=16.4, 5.9), 3.05(1H, dd, J=16.4, 9.8), 3.51(1H, m), 3.76(3H, s), 4.03(1H, dd, J=10.5, 9.5), 4.30(1H, ddd, J=10.5, 3.4, 2.0), 4.86(1H, br), 5.07(1H, br), 6.31(1H, d, J=2.4), 6.37(1H, dd, J=8.3, 2.4),6.64(1H, d, J=2.9), 6.70(1H, dd, J=8.8, 2.9), 6.79(1H, d, J=8.8), 6.95(1H, d, J=8.3)
E-55	mp 118-119℃
E-75	mp 45-47℃
E-76	mp 120-121℃
E-77	mp 85-87℃
E-78	mp 121-122℃

(Table 12-continued)

E-83	2.17(2H, dt, J=4.8, 6.4), 2.71(1H, dd, J=10.8, 16.4), 2.92(1H, ddd, J=2.0, 5.6, 16.4), 3.56-3.65 (1H, m), 3.77(3H, s), 3.78(3H, s), 3.83-4.00(4H, m), 4.02(1H, t, J=7.5), 4.15(1H, t, J=6.4), 4.30(1H, ddd, J=2.0, 3.2, 7.5), 5.08(1H, t, J=4.8), 6.08(2H, s), 6.88-6.94(2H, m), 7.14(1H, dd, J=1.6, 7.6), 7.20(1H, dt, J=1.6, 7.6)
E-84	1.72(3H, s), 1.77(3H, s), 2.71(1H, dd, J=10.4, 16.4), 2.92(1H, ddd, J=2.0, 5.6, 16.4), 3.59-3.68 (1H, m), 3.77(3H, s), 3.78(3H, s), 4.02(1H, t, J=10.0), 4.30(1H, ddd, J=2.0, 3.2, 10.0), 4.54(2H, d, J=6.4), 5.43-5.50(1H, m), 6.08(1H, d, J=2.4), 6.09(1H, d, J=2.4), 6.88-6.94(2H, m), 7.12-7.22(2H, m)
E-86	0.88(3H, t, J=7.3), 1.28-1.39(4H, m), 1.40-1.49(2H, m), 1.73-1.84(2H, m), 2.72(1H, dd, J=10.6, 16.4), 2.93(1H, ddd, J=1.9, 5.6, 16.4), 3.56-3.68(1H, m), 3.77(3H, s), 3.78(3H, s), 3.98(2H, t, J=6.4), 4.03(1H, t, J=10.0), 4.32(1H, ddd, J=1.9, 3.5, 10.0), 6.09(2H, s), 6.86-6.94(2H, m), 7.12-7.29(2H, m)
E-87	2.71(1H, dd, J=10.2, 16.4), 2.92(1H, ddd, J=1.8, 5.5, 16.4), 3.56-3.67(1H, m), 3.76(3H, s), 3.77(3H, s), 4.07(1H, t, J=10.4), 4.30(1H, ddd, J=1.8, 3.3, 10.4), 4.35(4H, s), 6.07(2H, s), 6.88-7.01(5H, m), 7.13-7.32(4H, m)
E-90	mp 95-96℃
E-93	mp 98-99℃
E-94	mp 91-93℃
F-21	mp 161-163℃
F-22	mp 123-124℃
F-23	1.70(3H, s), 3.78(3H, s), 4.43(1H, d, J=8.8), 4.84(1H, d, J=8.8), 4.97(1H, d, J=11.7), 5.01(2H, s), 5.02(1H, d, J=11.7), 6.36(1H, d, J=2.4), 6.44(1H, dd, J=8.5, 2.4), 6.48(1H, dd, J=8.3, 2.4), 6.64(1H, d, J=2.4), 7.04(1H, d, J=8.5), 7.04(1H, d, J=8.3), 7.29-7.41(10H, m)

(Table 12-continued)

F-35	mp 117-118℃
F-38	mp 155-158℃
F-39	1.80(3H, s), 3.75(3H, s), 3.78(3H, s), 4.41(1H, d, J=8.8), 4.77(1H, br), 4.81(1H, d, J=8.8), 5.02(1H, d, J=12.0), 5.06(1H, d, J=12.0), 6.04(1H, d, J=2.2), 6.09(1H, d, J=2.2), 6.26(1H, dd, J=8.3, 2.4), 6.49(1H, d, J=2.4), 6.82(1H, d, J=8.3), 7.26-7.41(5H, m)
F-40	1.81(3H, s), 3.75(3H, s), 3.77(3H, s), 4.42(1H, d, J=8.8), 4.82(1H, d, J=8.8), 5.00(2H, s), 5.02(1H, d, J=11.7), 5.06(1H, d, J=11.7), 6.03(1H, d, J=2.1), 6.09(1H, d, J=2.1), 6.42(1H, dd, J=8.7, 2.4), 6.63(1H, d, J=2.4), 6.88(1H, d, J=8.7), 7.26-7.41(10H, m)
H-11	mp 63-64℃
H-18	1.78(3H, s), 3.24(1H, d, J=15.5), 3.36(1H, d, J=15.5), 3.73(3H, s), 3.78(3H, s), 5.02(2H, s), 5.07(2H, s), 5.97(1H, d, J=2.0),6.15(1H, d, J=2.0), 6.53(1H, dd, J=8.6, 2.3), 6.63(1H, d, J=2.3), 7.30-7.42(10H, m), 7.52(1H, d, J=8.6)
H-29	1.65(3H, br), 1.72(3H, s), 1.75(3H, br), 3.22(2H, d, J=7.1), 3.37(1H, d, J=15.2), 3.51(1H, d, J=15.2), 3.67(3H, s), 3.78(3H, s), 5.03(2H, s), 5.06(2H, s), 5.14(1H, t, J=7.1), 6.27(1H, s), 6.55(1H, dd, J=8.6, 2.5), 6.66(1H, d, J=2.5), 7.32-7.44(10H, m), 7.53(1H, d, J=8.6)
J-8	mp 86-89℃
J-10	3.87(3H, s), 5.12(2H, d, J=1.3), 6.48(1H, d, J=8.2), 6.53(1H, d, J=8.2), 7.08(1H, t, J=8.2), 7.19(1H, brs), 7.27-7.49(5H, m).
J-15	mp 77-78℃
J-16	mp 86-87℃
J-39	3.80(3H, s), 3.84(3H, s), 5.10(2H, d, J=1.3), 6.08(1H, d, J=2.0), 6.12(1H, d, J=2.0), 7.11(1H, br s), 7.22-7.29(1H, m), 7.32-7.47(4H, m).

(Table 12-continued)

J-41	3.78(3H, s), 3.80(3H, s), 4.96(2H, d, J=1.2), 5.07(2H, s), 6.07(1H, d, J=2.1), 6.10(1H, d, J=2.1), 6.90-7.01(3H, m), 7.21-7.42(7H, m).
J-44	3.79(3H, s), 3.83(3H, s), 5.06(2H, d, J=1.3), 5.09(2H, s), 6.07(1H, d, J=2.1), 6.11(1H, d, J=2.1), 6.86-6.91(1H, m), 7.02-7.11(3H, m), 7.24-7.48(6H, m).
J-47	mp 81-83℃
K-27	mp 153-155℃
K-28	mp 106-107.5℃
K-30	mp 67-68℃
K-31	mp 90-92℃
K-36	1.38(9H, s), 3.86(3H, s), 3.92(3H, s), 6.32(1H, d, J=1.9), 6.68(1H, d, J=1.9), 6.93(1H, s), 7.04(2H, d, J=8.9), 7.68(2H, d, J=8.9)
K-37	mp 109-110℃
K-38	3.86(3H, s), 3.92(3H, s), 5.13(2H, s), 6.32(1H, d, J=2.0), 6.69(1H, d, J=1.3), 6.91(1H, ddd, J=7.9, 1.3, 1.0), 7.02(1H, s), 7.29-7.49(8H, m)
K-39	mp 81-82℃
K-41	mp 85.5-87℃
K-42	mp 113-115℃
K-43	mp 117-118℃
K-50	mp 95-96.5℃
K-53	mp 125-126℃
K-57	mp 125-126.5℃

(Table 12-continued)

K-58	3.50(3H, s), 3.53(3H, s), 3.86(3H, s), 3.93(3H, s), 5.20(2H, s), 5.34(2H, s), 6.32(1H, d, J=1.7), 6.69(1H, s), 6.80(1H, dd, J=8.5, 2.4), 6.93(1H, d, J=2.4), 7.20(1H, s), 7.88 (1H, d, J=8.5)
K-59	0.22(6H, s), 0.28(6H, s), 0.99(9H, s), 1.01(9H, s), 3.85(3H, s), 3.91(3H, s), 6.31(1H, d, J=2.0), 6.43(1H, d, J=2.3), 6.55(1H, dd, J=8.6, 2.3), 6.66(1H, dd, J=2.0, 0.8), 7.10(1H, d, J=0.8), 7.69(1H, d, J=8.6)
K-90	0.23(6H, s), 0.99(9H, s), 1.68(3H, s), 1.80(3H, s), 3.41(2H, d, J=6.9), 3.87(3H, s), 4.03(3H, s), 5.20(1H, m), 6.48(2H, m), 6.81(1H, s), 6.96(1H, d, J=0.8), 7.11(1H, s), 7.48(1H, d, J=9.1)
K-91	1.75-1.83(18H, m), 3.41(2H, d, J=6.9), 3.86(3H, s), 4.05(3H, s), 4.55(2H, d, J=6.8), 4.62(2H, d, J=6.4), 5.22(1H, m), 5.52(1H, m), 5.62(1H, m), 6.56(2H, m), 6.79(1H, d, J=0.8), 7.32(1H, d, J=0.8), 7.87(1H, d, J=8.9)
K-92	0.22(6H, s), 0.30(6H, s), 0.98(9H, s), 1.02(9H, s), 1.68(3H, s), 1.81(3H, s), 3.41(2H, d, J=6.9), 3.86(3H, s), 4.03(3H, s), 5.21(1H, m),6.44(1H, d, J=2.0), 6.56(1H, dd, J=8.6, 2.0), 6.80(1H, s), 7.21(1H, s), 7.75(1H, d, J=8.6)

(Drug product preparation example 1)

Examples of the preparation of compositions as medicine for cited below.

Preparation Example 1. Powdered medicine

For example, 5 g of the compound pursuant to the present invention, 800 g of lactose and 100 g of corn starch are blended in a blender to yield powdered medicine.

Preparation Example 2. Capsules

For example, 5 g of the compound pursuant to the present invention, 100 g of lactose, 50 g of corn starch and 2 g of magnesium stearate are blended. A total of 0.20 g of this is packed in a capsule to yield capsule medicine.

(Trial Example 1)

Table 13 presents the metabolic stimulating effects of the compound pursuant to the present invention on mouse myeloid cells. Trial compound at a concentration of 0.39 to 12.5 μg/ml was added to an RPM 11640 culture medium containing 2×10^5 cell/ml of BALB/c mouse myeloid cells, antibiotics, and 10% fetal bovine serum, followed by incubation for 5 days in 5% carbon dioxide at 37^0C. The mitrochondria metabolic activity of myeloid cells was measured by the MTT reduction method. The data in the table represent the degree of metabolism taking the degree of cell metabolism in the absence of specimen as 1. "N.T." in the table denotes absence of any trial.

(Table 13)

Compound No.	Metabolic acitivity Concentration added to culture medium (μ g/ml)					
No.	12.5	6.25	3.13	1.56	0.78	0.39
A-47	0.59	1.50	1.11	1.02	1.01	0.94
A-66	1.78	1.77	1.36	1.29	1.23	1.15
B-9	1.43	1.62	1.43	1.17	N.T.	N.T.
B-13	1.67	1.55	1.53	1.24	1.04	1.08
B-49	1.41	1.50	1.13	1.00	0.92	0.91
B-51	2.05	1.75	1.33	1.16	1.13	1.04
B-58	1.88	1.42	1.29	1.17	1.29	1.12
B-62	2.15	2.04	1.55	1.21	1.07	0.96
B-70	2.10	1.94	1.51	1.18	N.T.	N.T.
C-13	1.76	1.79	1.24	1.16	1.07	1.01
C-19	0.78	1.70	1.08	1.02	0.93	0.92
E-10	1.81	1.62	1.16	0.98	0.94	0.94
E-11	1.88	1.67	1.28	1.10	1.07	1.08
E-13	1.86	1.58	1.15	1.13	1.02	1.01
E-14	1.51	1.30	1.16	1.01	1.05	0.96
E-22	0.78	3.70	2.98	1.72	1.24	1.05
E-24	1.86	2.06	1.85	1.68	1.30	1.03
E-37	1.89	2.73	1.97	1.45	1.20	1.08
E-55	0.86	2.86	2.46	1.58	1.28	0.86
E-75	1.99	1.33	1.30	1.11	1.09	1.00
E-76	2.26	1.47	1.42	1.29	1.06	0.94
E-77	2.12	1.61	1.39	1.13	1.02	0.94
E-78	2.45	1.31	1.36	1.05	0.94	0.81
E-83	1.50	1.34	1.10	1.06	1.02	1.06
E-84	1.63	1.45	1.30	1.18	1.04	1.04
E-86	1.96	1.46	1.27	1.13	1.09	1.04
E-87	2.27	1.57	1.35	1.20	1.16	1.05
E-90	0.70	1.82	1.36	1.07	0.93	0.85
E-93	2.73	1.92	1.38	1.14	1.00	1.00
E-94	2.50	2.01	1.49	1.19	1.04	1.04
F-21	0.99	1.87	1.62	1.31	1.00	1.13
F-22	0.66	2.27	1.69	1.32	1.09	1.00
F-23	1.73	2.11	1.72	1.51	1.37	1.05
F-35	2.31	2.08	1.64	1.39	1.23	1.12
F-38	0.64	1.26	1.67	1.30	1.03	0.88
F-39	0.62	1.04	1.95	1.51	1.31	1.14
F-40	2.55	2.17	1.92	1.37	1.20	1.10

(Table 13-continued)

Compound No	Metabolic acitivity Concentration added to culture medium (μ g/ml)					
No.	12.5	6.25	3.13	1.56	0.78	0.39
H-11	2.68	1.68	1.30	1.14	1.07	0.88
H-18	2.29	1.61	1.45	1.30	N.T.	N.T.
H-29	1.76	1.62	1.47	1.20	N.T.	N.T.
J-8	1.59	1.33	1.11	1.00	0.93	0.93
J-10	1.59	1.55	1.25	1.05	1.03	0.86
J-11	1.35	1.32	1.02	1.02	1.01	1.01
J-14	0.77	1.32	1.06	0.93	0.91	0.83
J-15	1.80	1.58	1.14	1.00	0.91	0.94
J-16	1.89	1.51	1.31	1.06	0.97	0.88
J-39	1.56	1.46	1.27	1.11	1.10	1.02
J-41	1.39	1.64	1.46	1.19	1.06	1.10
J-44	1.99	1.57	1.35	1.22	1.04	1.06
J-47	1.93	1.92	1.53	1.52	1.19	1.03
K-27	0.90	0.64	1.41	1.56	1.42	1.20
K-28	0.58	1.76	1.23	1.11	1.06	1.02
K-30	1.50	1.38	1.20	1.09	1.06	1.03
K-31	1.84	1.31	0.91	0.88	0.94	0.88
K-36	1.62	1.43	1.22	1.19	1.09	1.08
K-37	2.13	1.51	1.31	1.19	1.09	1.05
K-38	1.62	1.44	1.20	1.06	1.01	1.03
K-39	1.41	1.67	1.53	1.19	1.08	1.05
K-41	1.82	1.24	1.07	0.97	0.96	0.98
K-42	2.03	1.38	0.99	0.91	0.85	0.85
K-43	1.93	1.51	1.41	1.28	1.11	1.09
K-50	1.54	1.42	1.30	1.25	1.18	1.08
K-53	0.36	1.81	1.47	1.19	1.02	0.98
K-57	1.92	1.52	1.41	1.00	1.10	1.17
K-58	0.95	1.80	1.29	1.08	N.T.	N.T.
K-59	1.79	1.40	1.29	1.19	1.08	1.00
K-90	N.T.	1.47	1.36	1.64	1.02	1.00
K-91	1.68	1.49	1.43	1.22	1.12	1.00
K-92	1.07	1.60	1.41	1.37	1.33	1.26

(Reference Example 1)

Single-dose administration safety

Compound (M) was dissolved in 0.5% carboxymethyl cellulose solution and orally administered at the peak dosage of 1000 mg/kg to five-week old CD-1 strain mice in an examination of single-dose administration safety. Observation was continued for 20 days following administration. No mice died even at the peak dosage level. Accordingly, the compound pursuant to the present invention was concluded to have high safety.

(Working Example 11)

Drug sensitivity restorative effects on resistant strain of Pseudomonas due to OprM overproduction

The minimum inhibitory concentration (MIC) of various types of antibiotics in the presence and absence of drug sensitivity restorative agents pursuant to the present invention (compound (M)) was measured on mutant strains (Na1B3 strain) experimental created with attenuated drug sensitivity due to OprM overproduction. Specifically, test bacteria were incubated for 24 hours at 37^0C in Mueller-Hinton broth (MHB) and the bacterial number was adjusted to 5×10^4/well. The MIC of each type of antibiotic was measured by the trace liquid dilution method using MHB. Calcium and magnesium were separately added to the respective MHBs so that the final concentrations would be 25 mg/L of Ca ion and 2.5 mg/L of Mg ions.

Compound (M) was added to a culture medium in which dimethyl sulfoxide had been dissolved so as to reach a concentration of 20 μg/ml. Each antibiotics was diluted in two-fold stages and the MIC was determined as the final concentration at which all bacterial growth was arrested. The antibiotics that were used were aztreonam (AZT), ceftazidime (CAZ), cefpirome (CPR), latamoxef (LMOX), cefsulodin (CFS), ofloxacin (OFLX), tetracycline (TC), and chloramphenicol (CP). Table 14 presents the results. Table 14 clearly indicates that the drug sensitivity of drug resistant Pseudomonas due to OprM overproduction was restored by using compound (M) or that compound with other drugs.

The results show that compound (M) has drug sensitivity restorative effects on drugs that participate in attenuated drug sensitivity caused by OprM overproduction . In addition, compound (M) did not exhibit any antibacterial activity against the Na1B3 strain or the OFR504 strain discussed below at concentrations of 100 μg/ml.

Table 14
Changes in MIC of the Na1B3 strain in the presence of 20 μg/ml of compound (M) to various types of drugs

	Amount of compound (M) added	
Drug	Without addition	20 μg/ml added
ceftazidime (CAZ)	3.13	1.56
cefpirome (CPR)	6.25	3.13
latamoxef (LMOX)	50	12.5
aztreonam (AZT)	25-12.5	3.13
cefsulodin (CFS)	6.25	3.13
ofloxacin (OFLX)	6.25	3.13
tetracycline (TC)	50	25
chloramphenicol (CP)	400	100

(Working Example 12)

The activity of compound (M) on various types of Pseudomonas was tested in accordance with Working Example 11. The bacterial strains used were Pseudomonas standard strain PA01 commonly used in genetic experiments, Pseudomonas laboratory mutant strain OFR504, and strain SLR-09. Strain OFR504 is the strain that expresses OprJ among the three types of Pseudomonas drug efflux pumps (OprM, OprJ, and OprN), and thus exhibits resistance to OPR, OFLX, and CP. Strain SLR-09 is the strain that exhibits resistance to CAZ, CPR, and LMOX through high production of β-lactamase. Table 15 presents the properties of the bacterial strains tested.

(Table 15)

	Na1B3	OFR504	SLR09	PA01
OprM	++	−	±	±
OprJ	−	++	−	−
β-lactamase	+	+	+++	+

− : No activity ± : Detectable +～+++ : Strong activity exhibited

Intensity of acitivity 「−」 < 「±」 < 「+」 < 「++」 < 「+++」

Table 16 presents the results
(Table 16)

Compound (M)	Na1B3		OFR504		SLR-09		PA01	
	Pre	Abs	Pre	Abs	Pre	Abs	Pre	Abs
CAZ	1.56	3.13	0.78	0.39	6.25	6.25	0.78	0.78
AZT	3.13	25-12.5	0.2	0.2	3.13	3.13	1.56	3.13
CPR	3.13	6.25	12.5	12.5	12.5	12.5	1.56	1.56
LMOX	12.5	50	1.56	1.56	50	50	6.25	12.5
CFS	3.13	6.25	0.78	0.78	3.13	3.13	1.56	1.56
OFLX	3.13	6.25	6.25	6.25	0.2	0.2	0.78	0.78
TC	25	50	>800	>800	400	400	25	25
CP	100	400	50	100	6.25	6.25	25	25

"Pre" indicates results in which compound (M) was present at the level of 20 μg/ml.

"Abs" indicates results in the compound (M) absent.

As Table 16 indicates, strain Na1B3 that had developed resistance due to OprM overproduction had its MIC restored through the addition of compound (M). Specifically, compound (M) has drug sensitivity restorative effects. However, no drug sensitivity restorative effects were exhibited in CPR- and OFLX resistance by strain OFR504, an OprJ overproduction-resistant strain, or in CAZ-, CPR- and LMOX resistance by strain SLR09, a resistant strain due to β-lactamase overproduction. This indicates that compound (M) specifically obstructs the OprM drug efflux pump. The drug sensitivity restorative effects observed in aforementioned working examples are effects of compound (M) rather than effects due to antibiotic addition or synergy. Specifically, the effects of compound (M) substantially for example, from those of antibiotic addition or synergy.

(Working Example 13)

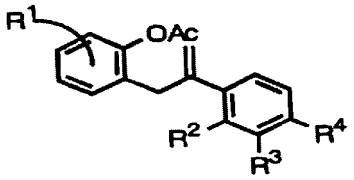
The drug sensitivity restorative effects of various compounds pursuant to the present invention were examined similarly to Working Example 11. Aztreonam (AZT) was the drug used and the MIC was measured under various conditions in the presence of 20 μg/ml of various types of compounds. Tables 17 to 21 present the results, which confirm that each type of compound had drug sensitivity restorative effects. The MIC of the control that used only aztreonam (AZT)

without any drug sensitivity restorative agents was 12.5 μg/ml. In addition, the MIC of compound (M) (compound K-59) as another control was measured and found to be 3.13 μg/ml.

The measured MIC is presented in the table in the "TI activity" column as an indicator of the drug sensitivity restorative effects. "TI activity" here is an abbreviation for Transporter Inhibitor activity.

As explained in Working Example 11, the MIC of compound (M) (compound number K-59) was 3.13 μg/ml.

(Table 17)



Compound No.	R^1	R^2	R^3	R^4	TI activity
C-16	5,7-(OMe)$_2$	H	OBzl	H	6.25 μg/ml
C-17	5,7-(OMe)$_2$	H	H	OBzl	6.25 μg/ml
C-19	5,7-(OMe)$_2$	Me	H	Me	6.25 μg/ml

Control AZT MIC : 12.5 μg/ml

MIC of compound (M) (K-59): 3.13 μg/ml

(12)特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2001 年2 月1 日 (01.02.2001)

PCT

(10) 国際公開番号
WO 01/07031 A1

(51) 国際特許分類[7]: A61K 31/085, 31/09, 31/12, 31/343, 31/352, 31/353, A61P 37/04, 43/00, C07D 307/79, 307/80, 311/64, C07C 43/215, 43/23, 49/84, 69/157

(21) 国際出願番号: PCT/JP00/05001

(22) 国際出願日: 2000 年7 月26 日 (26.07.2000)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:
特願平11/211399 1999 年7 月26 日 (26.07.1999) JP

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(81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) 指定国 (広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
— 国際調査報告書
— 請求の範囲の補正の期限前の公開であり、補正書受領の際には再公開される。

2文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(54) Title: BENZENE DERIVATIVES AND IMMUNOPOTENTIATING COMPOSITIONS OR DRUG-SENSITIVITY RESTORING AGENTS CONTAINING THE SAME

(54) 発明の名称: ベンゼン誘導体およびそれを含有する免疫賦活活性組成物

(57) Abstract: Specific compounds and compositions for preventing or treating diseases in association with immune function failures. Benzene derivative compounds, salts thereof or hydrates of the same which have immunopotentiating effects and are expected as efficacious as biological defense mechanism accelerators by exerting effects of potentiating the lymphocyte function and potentiating the bone marrow function.

(57) 要約:

本発明は、免疫機能の不全に伴う疾患を予防または治療するための、特定の化合物および組成物を提供することを課題とする。

本発明のベンゼン誘導体化合物もしくはその塩またはそれらの水和物は免疫賦活作用を有しており、リンパ球機能亢進作用、骨髄機能亢進作用を介し、生体防御機能亢進剤としての効果が期待できる。

本発明はまた、薬剤感受性回復剤を提供することも課題とする。

WO 01/07031 A1

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WO0107031

Publication No.	Publication date	Filing No.	Priority	Links
AU 6315300A	20010213	AU 6315300D 20000726	JP 0005001W 20000726 JP 21139999A 19990726	Espacenet
WO 0107031A1	20010201	JP 0005001W 20000726	JP 21139999A 19990726	Register (Epoline)

INPADOC Legal Status

WO0107031

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WO      000 5001W 2001-02-01AK    +DESIGNATED STATES Kind Code of Ref Document A1
        000 5001W 2001-02-01AK    +DESIGNATED STATES Designated State(s) AE AG
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                  DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
                  KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT
                  RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
WO      000 5001W 2001-02-01AL    +DESIGNATED COUNTRIES FOR REGIONAL PATENTS
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WO      000 5001W 2001-03-28121    EP: THE EPO HAS BEEN INFORMED BY WIPO THAT EP
                  WAS DESIGNATED IN THIS APPLICATION
        000 5001W 2001-04-26DFPE   REQUEST FOR PRELIMINARY EXAMINATION FILED
                  PRIOR TO EXPIRATION OF 19TH MONTH FROM PRIORITY DATE (PCT
                  APPLICATION FILED BEFORE 20040101)
WO      000 5001W 2001-10-15ENP    ENTRY INTO THE NATIONAL PHASE IN: Ref Country
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        000 5001W 2001-10-15ENP    ENTRY INTO THE NATIONAL PHASE IN: Ref
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        000 5001W 2001-10-15ENP    ENTRY INTO THE NATIONAL PHASE IN: Format of
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        000 5001W 2002-05-23REG    REFERENCE TO NATIONAL CODE Ref Legal Event
                  Code 8642 (IMPACT ABOLISHED FOR DE - I.E. PCT APPL. NOT ENT. GERMAN PHASE)
WO      000 5001W 2002-09-18122   -EP: PCT  APP. NOT ENT. EUROP. PHASE
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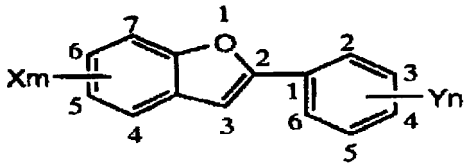
No English Equivalents

（表１０）



(I-K)

No.	Xm	Yn
K-1	H	2,4-(OTBS)$_2$
K-2	4-OMe	4-OH
K-3	4-OMe	4-OBzl
K-4	4-OMe	2,4-(OBzl)$_2$
K-5	4-OMe	2,4-(OMOM)$_2$
K-6	4-OMe	2,4-(OTBS)$_2$
K-7	5-OMe	4-OH
K-8	5-OMe	4-OBzl
K-9	5-OMe	2,4-(OBzl)$_2$
K-10	5-OMe	2,4-(OMOM)$_2$
K-11	5-OMe	2,4-(OTBS)$_2$
K-12	6-OMe	4-OH
K-13	6-OMe	4-OBzl
K-14	6-OMe	2,4-(OBzl)$_2$
K-15	6-OMe	2,4-(OMOM)$_2$
K-16	6-OMe	2,4-(OTBS)$_2$
K-17	7-OMe	4-OH
K-18	7-OMe	4-OBzl
K-19	7-OMe	2,4-(OBzl)$_2$
K-20	7-OMe	2,4-(OMOM)$_2$
K-21	7-OMe	2,4-(OTBS)$_2$
K-22	4,5-(OMe)$_2$	4-OH
K-23	4,5-(OMe)$_2$	4-OBzl
K-24	4,5-(OMe)$_2$	2,4-(OBzl)$_2$
K-25	4,5-(OMe)$_2$	2,4-(OMOM)$_2$
K-26	4,5-(OMe)$_2$	2,4-(OTBS)$_2$
K-27	4,6-(OH)$_2$	2,4-(OTBS)$_2$
K-28	4-OH-6-OMe	2,4-(OTBS)$_2$
K-29	4-OMe-6-OH	2,4-(OTBS)$_2$
K-30	4,6-(OMe)$_2$	H

（表10続き）

K-31	4,6-$(OMe)_2$	2-Cl
K-32	4,6-$(OMe)_2$	2-OH
K-33	4,6-$(OMe)_2$	3-OH
K-34	4,6-$(OMe)_2$	4-OH
K-35	4,6-$(OMe)_2$	2-OBu^t
K-36	4,6-$(OMe)_2$	4-OBu^t
K-37	4,6-$(OMe)_2$	2-OBzl
K-38	4,6-$(OMe)_2$	3-OBzl
K-39	4,6-$(OMe)_2$	4-OBzl
K-40	4,6-$(OMe)_2$	2-(2-ClBzlO)
K-41	4,6-$(OMe)_2$	2-(3-ClBzlO)
K-42	4,6-$(OMe)_2$	2-(4-ClBzlO)
K-43	4,6-$(OMe)_2$	2-OPh
K-44	4,6-$(OMe)_2$	2-CO_2H
K-45	4,6-$(OMe)_2$	2-CO_2Me
K-46	4,6-$(OMe)_2$	2-$CO_2{}^iPr$
K-47	4,6-$(OMe)_2$	2-CO_2Bzl
K-48	4,6-$(OMe)_2$	2-NH_2
K-49	4,6-$(OMe)_2$	2-N=CHPh
K-50	4,6-$(OMe)_2$	2-NHBzl
K-51	4,6-$(OMe)_2$	2-NO_2
K-52	4,6-$(OMe)_2$	2,4-$(OH)_2$
K-53	4,6-$(OMe)_2$	2-OH-4-OBzl
K-54	4,6-$(OMe)_2$	2-OH-4-OTBS
K-55	4,6-$(OMe)_2$	2-OBzl-4-OH
K-56	4,6-$(OMe)_2$	2,4-$(OMe)_2$
K-57	4,6-$(OMe)_2$	2,4-$(OBzl)_2$
K-58	4,6-$(OMe)_2$	2,4-$(OMOM)_2$
K-59	4,6-$(OMe)_2$	2,4-$(OTBS)_2$
K-60	4,6-$(OMe)_2$	2,4-$(OCH_2CO_2H)_2$
K-61	4,6-$(OMe)_2$	2,4-$(OCH_2CO_2Et)_2$
K-62	4,6-$(OMe)_2$	2,4-$(OCH_2CO_2Na)_2$
K-63	4,6-$(OMe)_2$	2,4-(4-picolyloxy)$_2$
K-64	4,7-$(OMe)_2$	4-OH
K-65	4,7-$(OMe)_2$	4-OBzl

,7,296)

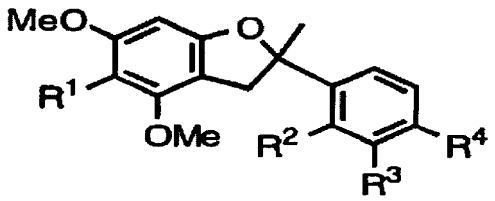
（表10続き）

K-66	4,7-$(OMe)_2$	2,4-$(OBzl)_2$
K-67	4,7-$(OMe)_2$	2,4-$(OMOM)_2$
K-68	4,7-$(OMe)_2$	2,4-$(OTBS)_2$
K-69	5,6-$(OMe)_2$	4-OH
K-70	5,6-$(OMe)_2$	4-OBzl
K-71	5,6-$(OMe)_2$	2,4-$(OBzl)_2$
K-72	5,6-$(OMe)_2$	2,4-$(OMOM)_2$
K-73	5,6-$(OMe)_2$	2,4-$(OTBS)_2$
K-74	5,7-$(OMe)_2$	4-OH
K-75	5,7-$(OMe)_2$	4-OBzl
K-76	5,7-$(OMe)_2$	2,4-$(OBzl)_2$
K-77	5,7-$(OMe)_2$	2,4-$(OMOM)_2$
K-78	5,7-$(OMe)_2$	2,4-$(OTBS)_2$
K-79	6,7-$(OMe)_2$	4-OH
K-80	6,7-$(OMe)_2$	4-OBzl
K-81	6,7-$(OMe)_2$	2,4-$(OBzl)_2$
K-82	6,7-$(OMe)_2$	2,4-$(OMOM)_2$
K-83	6,7-$(OMe)_2$	2,4-$(OTBS)_2$
K-84	4,6-$(OMe)_2$-5-Me	4-OH
K-85	4,6-$(OMe)_2$-5-Me	4-OBzl
K-86	4,6-$(OMe)_2$-5-Me	2,4-$(OBzl)_2$
K-87	4,6-$(OMe)_2$-5-Me	2,4-$(OMOM)_2$

（表１０続き）

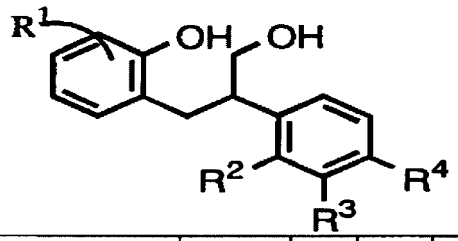
K-88	4,6-$(OMe)_2$-5-Me	2,4-$(OTBS)_2$
K-89	4,6-$(OMe)_2$-5-prenyl	2-prenyloxy-4-OH
K-90	4,6-$(OMe)_2$-5-prenyl	2-OH-4-OTBS
K-91	4,6-$(OMe)_2$-5-prenyl	2,4-$(prenyloxy)_2$
K-92	4,6-$(OMe)_2$-5-prenyl	2,4-$(OTBS)_2$
K-93	4,6-$(OMe)_2$-5-prenyl	2,4-$(OH)_2$

(Table 18)



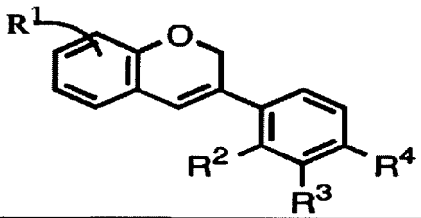
Compound No.	R^1	R^2	R^3	R^4	TI activity
H-28	Prenyl	OH	H	OH	3.13 μg/ml

(Table 19)



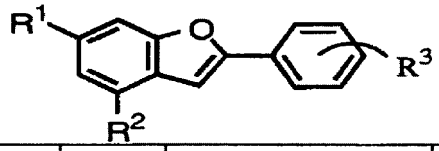
Compound No.	R^1	R^2	R^3	R^4	TI activity
D-11	5,7-$(OMe)_2$	Ph	H	H	6.25 μg/ml
D-12	5,7-$(OMe)_2$	H	H	Ph	6.25 μg/ml
D-13	5,7-$(OMe)_2$	OBzl	H	H	6.25 μg/ml
D-16	5,7-$(OMe)_2$	Me	H	Me	6.25 μg/ml

(Table 20)



Compound No.	R^1	R^2	R^3	R^4	TI activity
J-2	H	H	NO_2	H	6.25 μg/ml
J-39	5,7-$(OMe)_2$	H	H	H	6.25 μg/ml
J-41	5,7-$(OMe)_2$	OBzl	H	H	6.25 μg/ml
J-14	5-OMe	H	NO_2	H	6.25 μg/ml
J-26	8-OMe	CF_3	H	H	6.25 μg/ml
J-25	8-OMe	H	H	H	6.25 μg/ml
J-30	8-OMe	H	NO_2	H	6.25 μg/ml
J-31	8-OMe	H	H	F	6.25 μg/ml

(Table 21)



Compound No.	R^1	R^2	R^3	TI activity
K-59	OMe	OMe	2',4'-$(OTBS)_2$	6.25 μg/ml
K-54	OMe	OMe	2'-OH 4'-OTBS	6.25 μg/ml
K-33	OMe	OMe	3'-OH	6.25 μg/ml

Field of Industrial Utilization

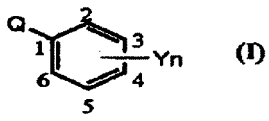
(Effects of Invention)

The present invention provides novel benzene derivatives through the use of which an effect as a biological defense mechanism accelerator is anticipated via lymphocyte function acceleration effects and bone marrow function acceleration effects. Furthermore, a useful drug sensitivity restorative agent is provided via these novel benzene derivatives.

The drug sensitivity restorative agents pursuant to the present invention exhibit outstanding drug sensitivity restorative effects and, because of their high safety, are extremely useful on infections attributable to multi-drug resistant Pseudomonas.

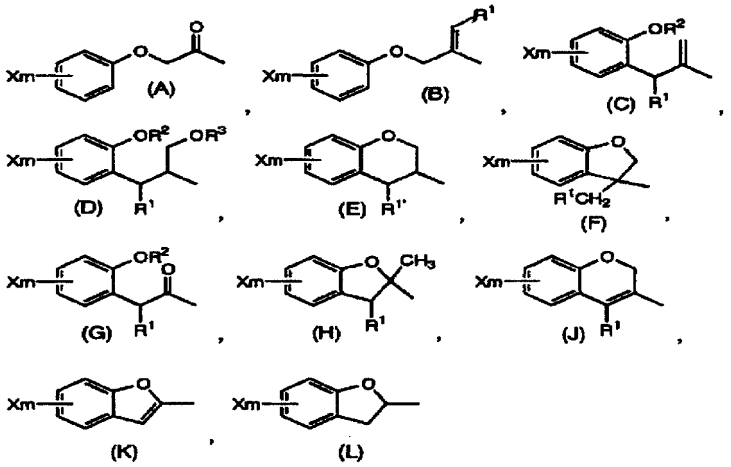
Claims

1. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I):



(I)

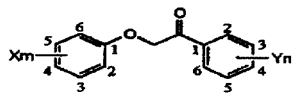
[In the formula, Q represents the following



(In the formula, X represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
R^1 and $R^{1'}$ represent hydrogens or alkyls;
R^2 and R^3 represent hydrogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, tri-substituted silyls, optionally substituted acyls, optionally substituted amino carbonyls or mono-substituted sulfonyls;
and m represents an integer of 0 to 4);

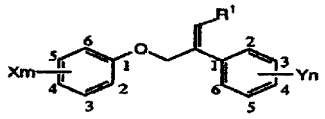
Y represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
and n represents an integer of 0 to 5;
however, position 5 and position 7 Xm, position 2 and position 4 Yn in formula (E) may all be identical or different hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, or tri-substituted silyloxys, in which cases $R^{1'}$ is not a hydrogen].

2. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-A):



(I-A)

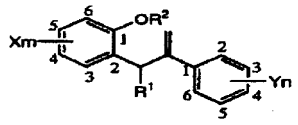
(In the formula, X, Y, m and n have the same significance as in Claim 1).
3. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-B):



(I-B)

(In the formula, X, Y, R^1, m and n have the same significance as in Claim 1).

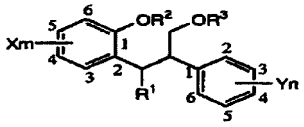
4. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-C):



(I-C)

(In the formula, X, Y, R^1, R^2, m and n have the same significance as in Claim 1).

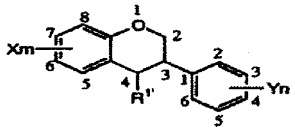
5. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-D):



(I-D)

(In the formula, X, Y, R^1, R^2, R^3, m and n have the same significance as in Claim 1).

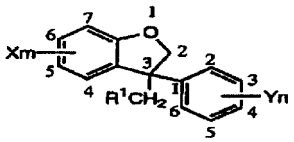
6. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-E):



(I-E)

(In the formula, X, Y, R^1, m and n have the same significance as in Claim 1).

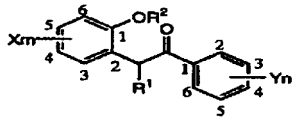
7. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-C):



(I-F)

(In the formula, X, Y, R^1, m and n have the same significance as in Claim 1).

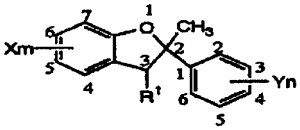
8. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-G):



(I-G)

(In the formula, X, Y, R^1, R^2, m and n have the same significance as in Claim 1).

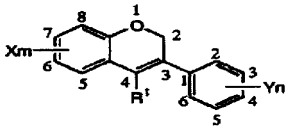
9. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-H):



(I-H)

(In the formula, X, Y, R^1, R^2, m and n have the same significance as in Claim 1).

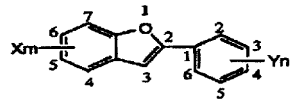
10. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-J):



(I-J)

(In the formula, X, Y, R^1, m and n have the same significance as in Claim 1).

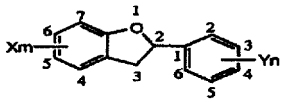
11. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-K):



(I-K)

(In the formula, X, Y, m and n have the same significance as in Claim 1).

12. A composition having immunopotentiating effects containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-L):



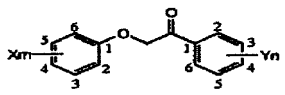
(I-L)

(In the formula, X, Y, m and n have the same significance as in Claim 1).

13. The compositions stated in Claim 1 wherein X represents halogens, alkyls, alkenyls, hydroxys, optionally substituted alkoxys, Y represents halogens, alkyls, haloalkyls, aryls, hydroxys, optionally substituted alkoxys, alkenyloxys, tri-substituted silyloxys, or nitros, and m represents an integer of 0 to 3 while n represents an integer of 0 to 2.

14. The compositions stated in Claim 1 wherein X represents chloros, methyls, hydroxys, methoxys or prenyloxys, Y represents fluoros, methyls, trifluoromethyls, phenyls, hydroxys, methoxys, prenyloxys, n-hexyloxys, 2-phenoxyethoxys, 2-(1,3-dioxoran-2-yl) ethoxys, benzyloxys, or nitros, while m represents an integer of 0 to 3 and n represents an integer of 0 to 2.

15. Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-A):

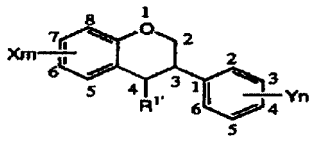


(I-A)

(In the formula, X represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
Y represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;

m represents an integer of 1 to 4 and n represents an integer of 1 to 5)

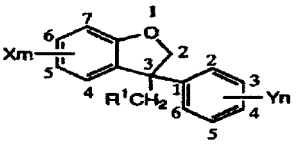
16. Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-E):



(I-E)

(In the formula, X, Y, R^1, m and n have the same significance as in Claim 15, $R^{1'}$ represents hydrogens or alkyls, but position 5 and position 7 Xm, position 2 and position 4 Yn in formula (I-E) may all be identical or different hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys or tri-substituted silyloxys, in which cases $R^{1'}$ is not a hydrogen).

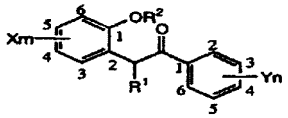
17. Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-F):



(I-F)

(In the formula, X, Y, m and n have the same significance as in Claim 15, $R^{1'}$ represents hydrogens or alkyls).

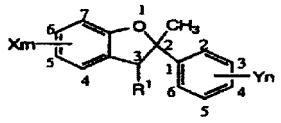
18. Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-G):



(I-G)

(In the formula, X, Y, m, n and R^1 have the same significance as in Claim 15, R^2 represents optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, tri-substituted silyls, optionally substituted acyls, optionally substituted amino carbonyls, or mono-substituted sulfonyls).

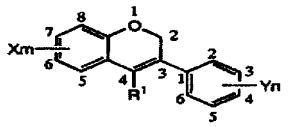
19. Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-H):



(I-H)

(In the formula, X, Y, m and n have the same significance as in Claim 15, R^1 has the same significance as in Claim 17.

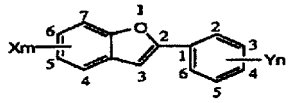
20. Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-J):



(I-J)

(In the formula, X, Y, m and n have the same significance as in Claim 15, R^1 has the same significance as in Claim 17.

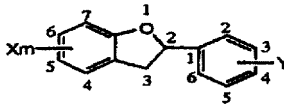
21. Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-K):



(I-K)

(In the formula, X, Y, m and n have the same significance as in Claim 15, but Yn is not 4-dihydroxy when Xm represents 4,6-dimethoxy-5-prenyl).

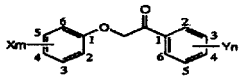
22. Compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formula (I-L):

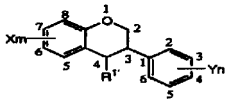


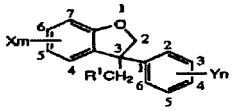
(I-L)

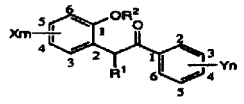
(In the formula, X, Y, m and n have the same significance as in Claim 15.

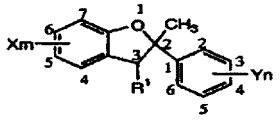
23. Compounds represented by the following formulas, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof,
general formulas (I-A), (I-E), (I-F), (I-G), (I-H), (I-J), (I-K), or (I-L).

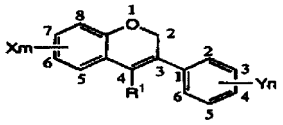

(I-A)

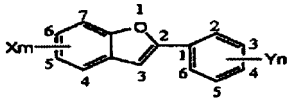

(I-E)

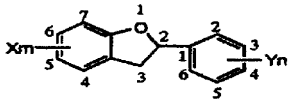

(I-F)


(I-G)


(I-H)


(I-J)


(I-K)


(I-L)

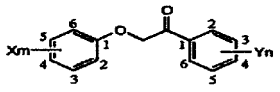
(In the formula, X represents halogens, alkyls, alkenyls, hydroxys, optionally substituted alkoxys; Y represents halogens, alkyls, haloalkyls, aryls, hydroxys, optionally substituted alkoxys, alkenyloxys, tri-substituted silyloxys, or nitros;
m represents an integer of 0 to 3,
n represents an integer of 0 to 2;
$R^{1'}$ represents hydrogens or alkyls, however, position 5 and position 7 Xm as well as position 2 and position 4 Yn in formula (I-E) may be identical or different hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, in which cases $R^{1'}$ is not hydrogen;
R^{1} represents hydrogens or alkyls;

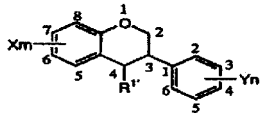
R^2 represents optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, tri-substituted silyls, optionally substituted acyls, optionally substituted amino carbonyls, or mono-substituted sulfonyls;
however, when Xm in formula (I-K) is 4,6-dimethoxy-5-prenyl, Yn is not 2,4-dihydroxy).

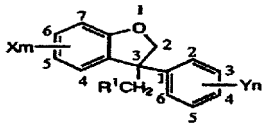
24. Compounds presented in Claim 23, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof wherein X represents chloros, methyls, hydroxys, methoxys, or prenyloxys, Y represents fluoros, methyls, trifluoromethyls, phenyls, hydroxys, methoxys, prenyloxys, n-hexyloxys, 2-phenoxyethoxys, 2-(1,3-dioxolan-2-yl) ethoxys, benzyloxys, or nitros, m represents an integer of 0 to 3, n represents an integer of 0 to 2.

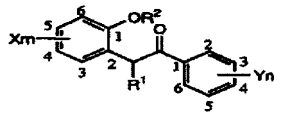
25. Compounds presented in Claim 23, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof wherein Xm represents 4-chloro, 3-methoxy, 4-methoxy, 5-methoxy, 3,5-dimethoxy, or 3,5-dimethoxy-4-prenyloxy, Yn represents 4-fluoro, 4-methyl, 2-trifluoromethyl, 2,4-dimethyl, 2-phenyl, 4-phenyl, 2-hydroxy, 2,4-dihydroxy, 2-prenyloxy, 2-n-hexyloxy, 2-benzyloxy, 3-benzyloxy, 4-benzyloxy, 2-benzyloxy-4-hydroxy, 2,4-dibenzyloxy, 3-(1,3-dioxolan-2-yl) ethoxy, 3- phenoxyethoxy, or 3-nitro (however, the names of the individual substitution positions conform with the nomenclature method of the substitution positions in general formula (I-A).

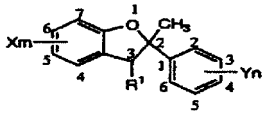
26. A composition containing compounds represented by the following formulas, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof as the active ingredient: general formulas (I-A), (I-E), (I-F), (I-G), (I-H), (I-J), (I-K), or (I-L).

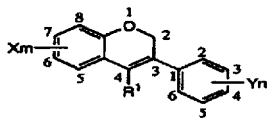

(I-A)

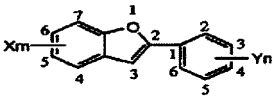

(I-E)

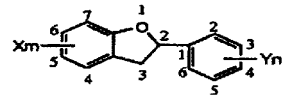

(I-F)


(I-G)


(I-H)


(I-J)


(I-K)

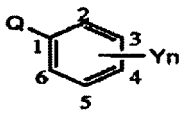

(I-L)

(In the formula, X represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, mono-substituted sulfinyls, mono-substituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
Y represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, mono-substituted sulfinyls, mono-substituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
m represents an integer of 1 to 4;
n represents an integer of 1 to 5;
$R^{1'}$ represents hydrogens or alkyls, however, position 5 and position 7 Xm as well as position 2 and position 4 Yn in formula (I-E) may be identical or different hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, in which cases $R^{1'}$ is not hydrogen;

R^1 represents hydrogens or alkyls;
R^2 represents optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, tri-substituted silyls, optionally substituted acyls, optionally substituted amino carbonyls, or mono-substituted sulfonyls).

27. The compositions presented in Claim 26 that have immunopotentiating effects.

28. The use of compounds of general formula (I), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof to produce compositions having immunopotentiating effects:

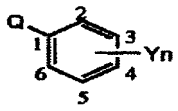


(I)

(In the formula, Q, Y, and n have the same significance as in Claim 1).

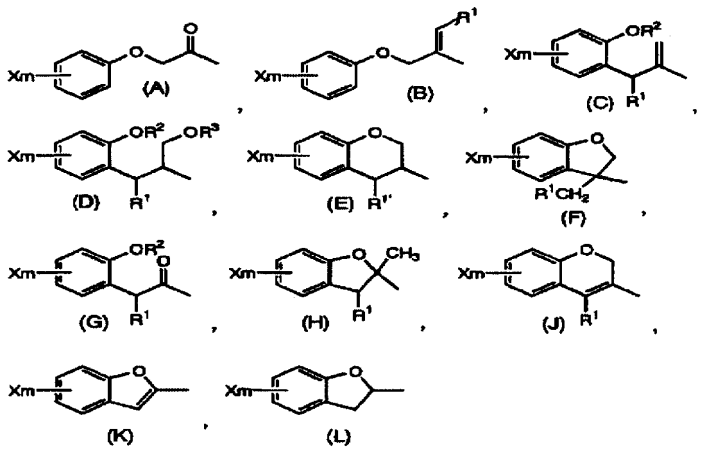
29. A method of incorporating the step of administering the compositions stated in Claim 1 to an subject of examination in the method of activating the immunity of said subject of examination.

30. Drug sensitivity restorative agents containing compounds represented by the following formula, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof.
general formula (I)



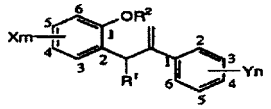
(I)

[In the formula, Q represents the following



(In the formula, X represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, mono-substituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
R^1 and $R^{1'}$ represent hydrogens or alkyls;
R^2 and R^3 represent hydrogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, tri-substituted silyls, optionally substituted acyls, optionally substituted amino carbonyls or mono-substituted sulfonyls;
and m represents an integer of 0 to 4);
Y represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
and n represents an integer of 0 to 5; however, position 5 and position 7 Xm as well as position 2 and position 4 Yn in formula (E) may all be identical or different hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, or tri-substituted silyloxys, in which cases $R^{1'}$ is not a hydrogen].

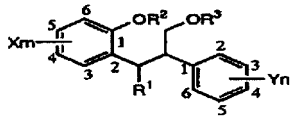
31. Drug sensitivity restorative agents containing compounds represented by general formula (I-C), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof



(I-C)

(In the formula, X, Y, R^1, R^2, m and n have the same significance as in Claim 30).

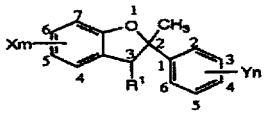
32. Drug sensitivity restorative agents containing compounds represented by general formula (I-D), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof



(I-D)

(In the formula, X, Y, R^1, R^2, R^3, m and n have the same significance as in Claim 30).

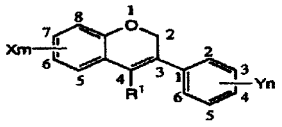
33. Drug sensitivity restorative agents containing compounds represented by general formula (I-H), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof



(I-H)

(In the formula, X, Y, R^1, m and n have the same significance as in Claim 30).

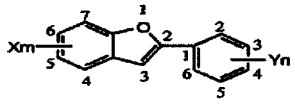
34. Drug sensitivity restorative agents containing compounds represented by general formula (I-J), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof



(I-J)

(In the formula, X, Y, R^1, m and n have the same significance as in Claim 30).

35. Drug sensitivity restorative agents containing compounds represented by general formula (I-K), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof

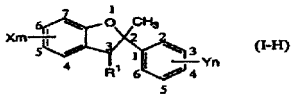

(I-K)

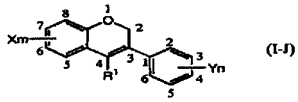
(In the formula, X, Y, m and n have the same significance as in Claim 30).

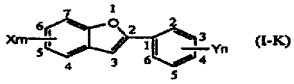
36. Drug sensitivity restorative agents presented in Claim 30 wherein X represents halogens, alkyls, alkenyls, hydroxys, optionally substituted alkoxys, Y represents halogens, alkyls, haloalkyls, aryls, hydroxys, optionally substituted alkoxys, alkenyloxys, tri-substituted silyloxys, or nitros, and m represents an integer of 0 to 3 while n represents an integer of 0 to 2.

37. Drug sensitivity restorative agents presented in Claim 30 wherein X represents chloros, methyls, hydroxys, methoxys, or prenyloxys, Y represents fluoros, methyls, trifluoromethyls, phenyls, hydroxys, methoxys, prenyloxys, n-hexyloxys, 2-phenoxyethoxys, 2-(1,3-dioxolan-2-yl) ethoxys, benzyloxys, or nitros, m represents an integer of 0 to 3, n represents an integer of 0 to 2.

38. Drug sensitivity restorative agents containing compounds represented by the following formulas, prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof as the active ingredient:
general formulas (I-H), (I-J), or (I-K)


(I-H)


(I-J)


(I-K)

(In the formula, X represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally substituted alkylthios, optionally substituted arylthios, mono-substituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
Y represents halogens, optionally substituted alkyls, optionally substituted alkenyls, optionally substituted alkynyls, optionally substituted aryls, hydroxys, optionally substituted alkoxys, optionally substituted alkenyloxys, optionally substituted alkynyloxys, optionally substituted aryloxys, optionally substituted acyloxys, tri-substituted silyloxys, mercaptos, optionally

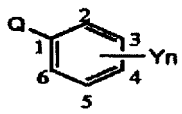
substituted alkylthios, optionally substituted arylthios, monosubstituted sulfinyls, monosubstituted sulfonyls, optionally substituted aminos, optionally substituted acyls, optionally substituted amino carbonyls, hydroxy carbonyls, optionally substituted alkoxy carbonyls, cyanos, nitros, or tri-substituted silyls;
m represents an integer of 1 to 4;

n represents an integer of 1 to 5;
R^1 represents hydrogens or alkyls;
however, when Xm in formula (I-K) is 4,6-dimethoxy-5-prenyl, Yn is not 2,4-dihydroxy).

39. Drug sensitivity restorative agents presented in Claim 30 that restore the sensitivity of Pseudomonas to drugs.

40. Drug sensitivity restorative agents presented in Claim 30 that restore sensitivity that had been reduced by OprM overproduction.

41. The use of compounds of general formula (I), prodrugs thereof, pharmaceutically acceptable salts thereof, or solvates thereof to produce drug sensitivity restorative agents:



(I)

(In the formula, Q, Y, and n have the same significance as in Claim 30).

42. A method of incorporating the step of administering the drug sensitivity restorative agents stated in Claim 30 to an subject of examination in the method of restoring the sensitivity of said subject of examination to drugs.